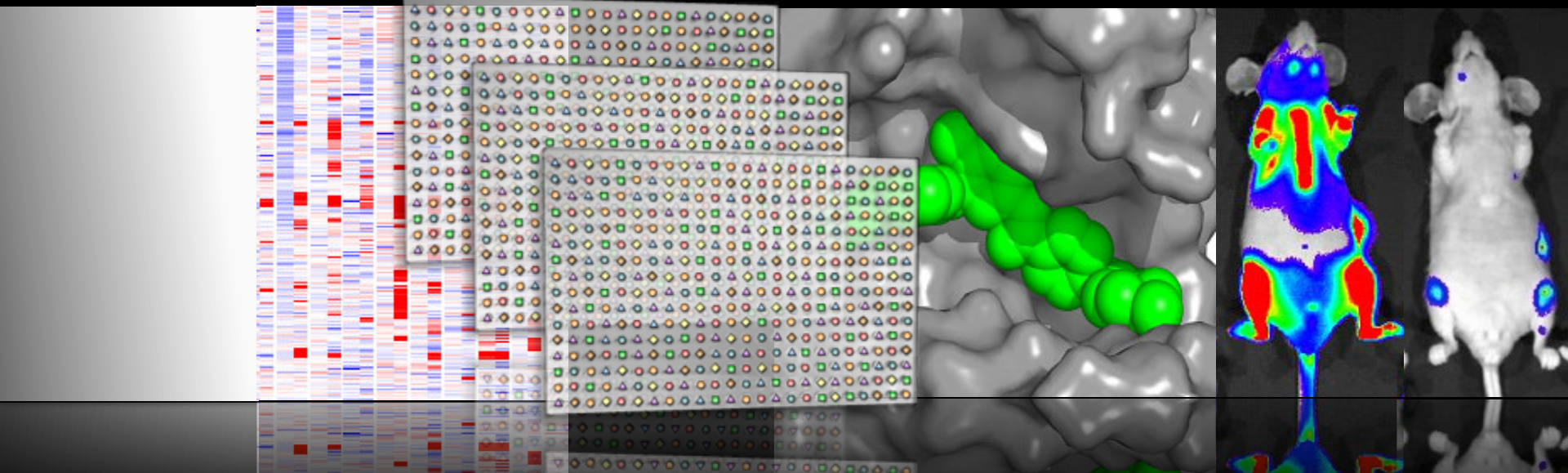


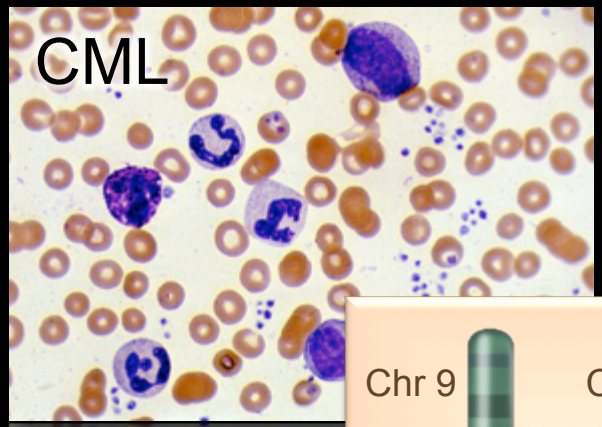
The genetic basis for cancer therapeutics
– the opportunity and the obstacles

The Cancer Genome Atlas Project
November 27th, 2012

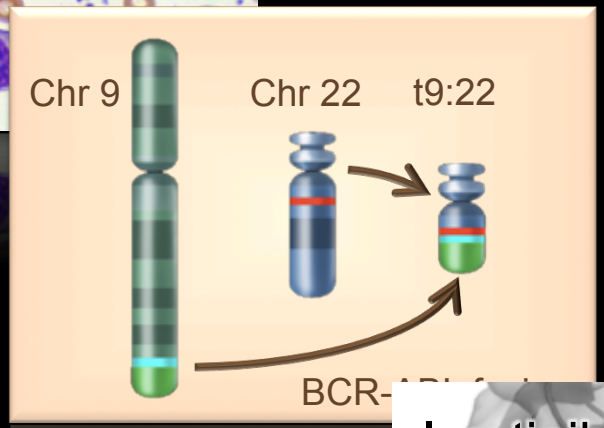
Bill Sellers, VP/Global Head Oncology
Novartis Institutes For BioMedical Research

The Paradigm Shift: CML and imatinib

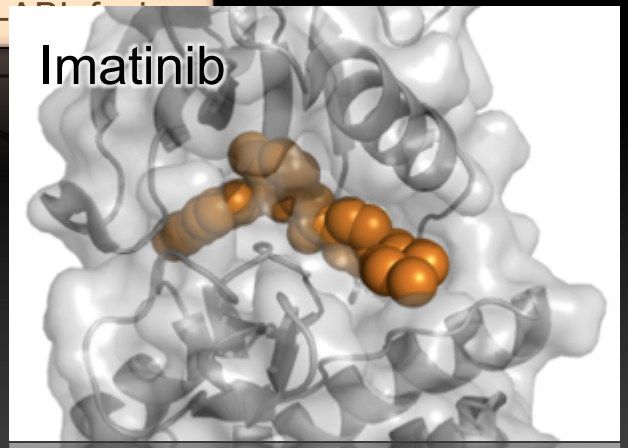
Disease



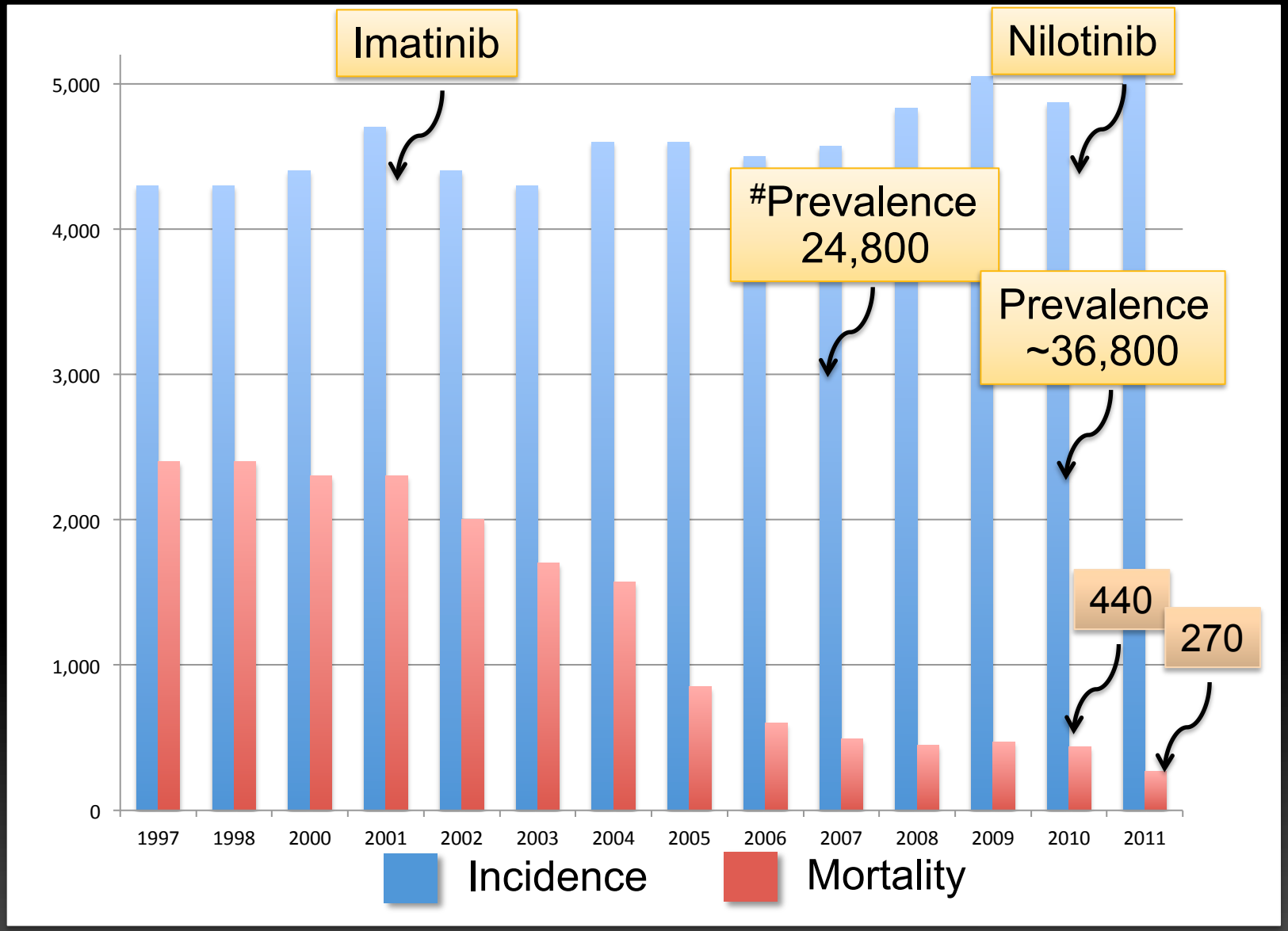
Pathogenesis



Target-based drug discovery

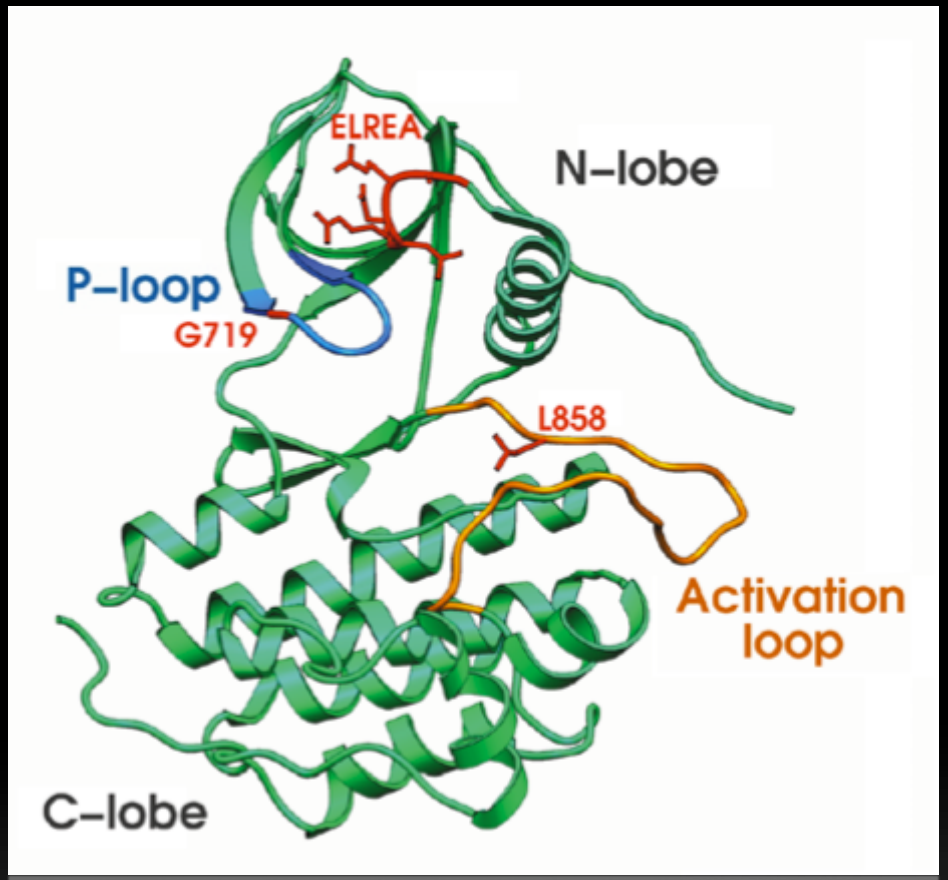


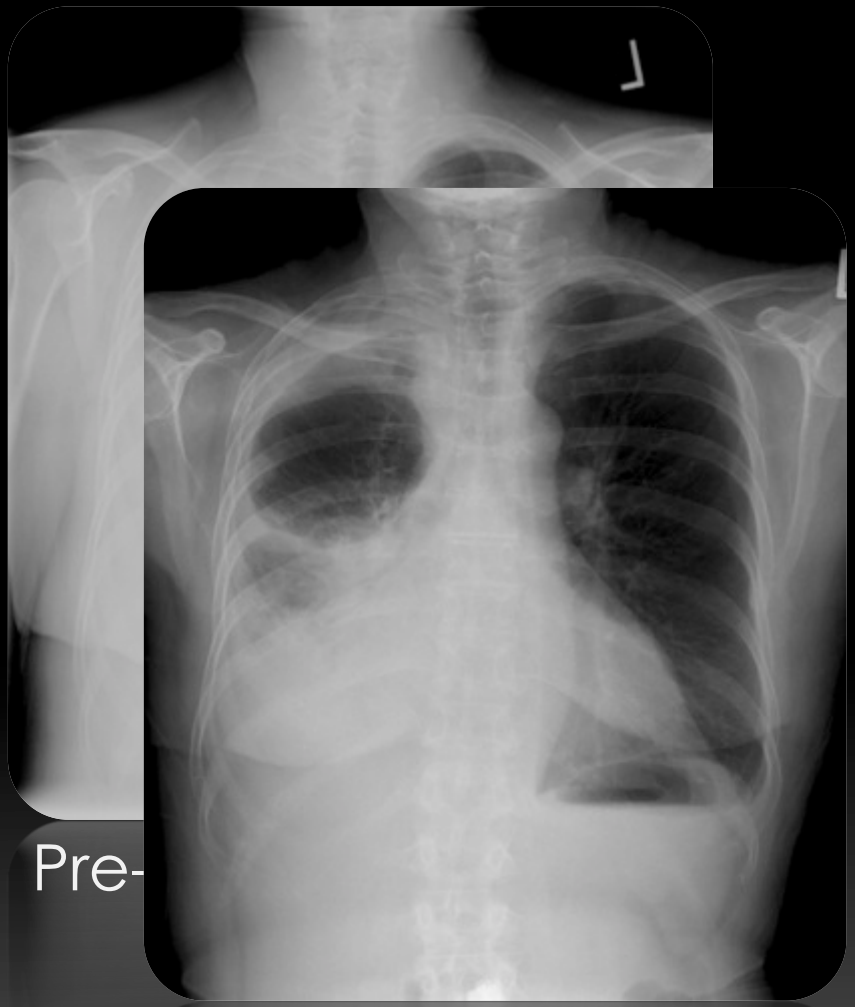
The genetic paradigm validated:
-a *dramatic reduction in the mortality from CML since 2001*



Ca Journal Statistics

Mutations in the kinase domain of EGFR

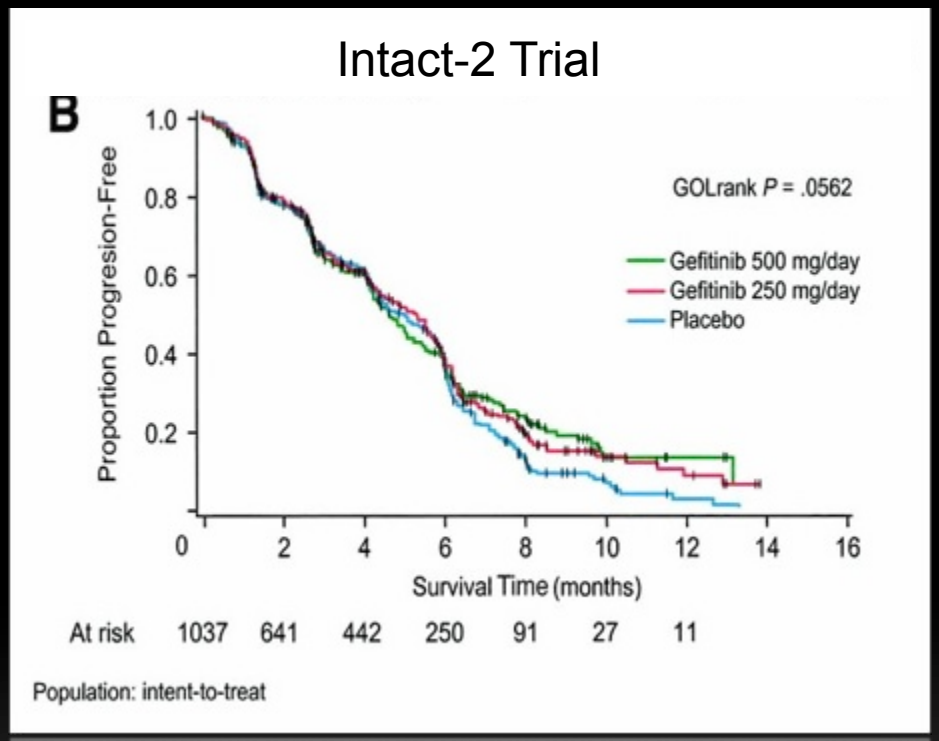




Paez et al Science 2004, Lynch et al NEJM 2004, Pao et al PNAS 2004

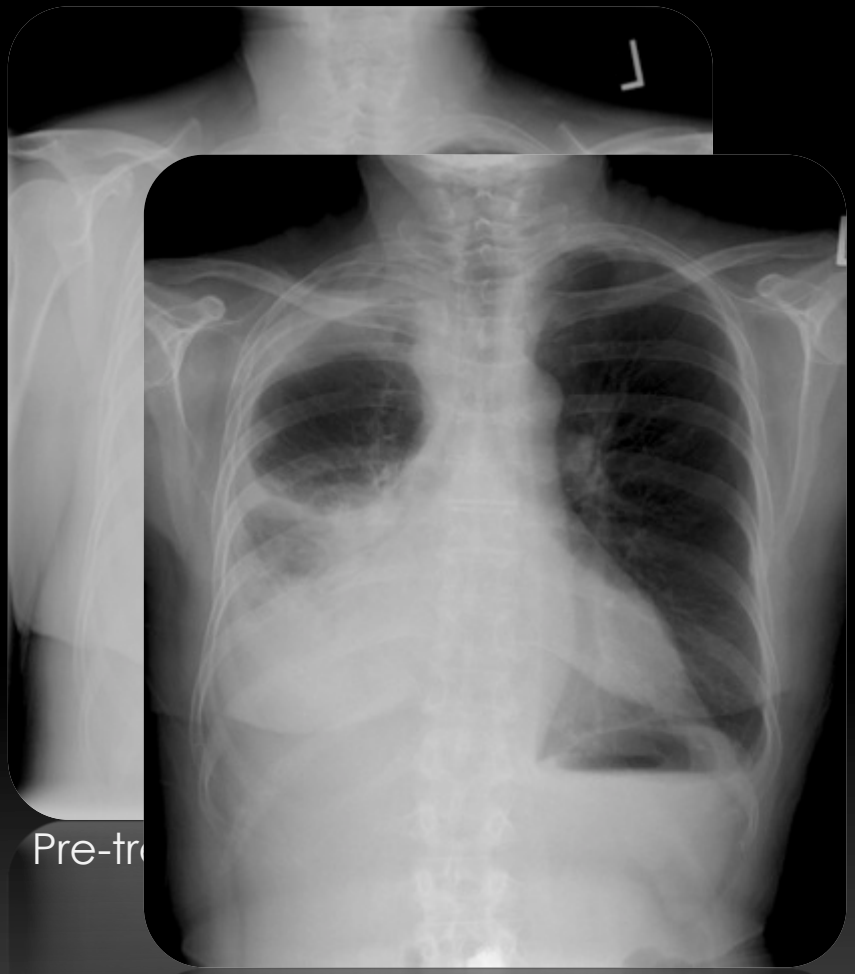
Two models of drug development

A



Empiric

B



Pathogenesis-driven

Two models of drug development

What are the problems or impediments to Plan B?

#1. We do not know the complete compendium of genetic alterations in cancer.

We need to “finish” the atlas….

…….. and we have a long way to go.

-all cancer types and subtypes

-pre-malignant lesions, early stage cancer, metastatic cancer….

-completion to the extent that we can robustly define functionally redundant, cooperating and antagonistic genetic events.

Two models of drug development

What are the problems or impediments to Plan B?

#1. We do not know the complete compendium of genetic alterations in cancer.

#2. Most known genetic alterations have not led directly to drug candidates.

Problem #2a Most oncogenes are not "druggable"

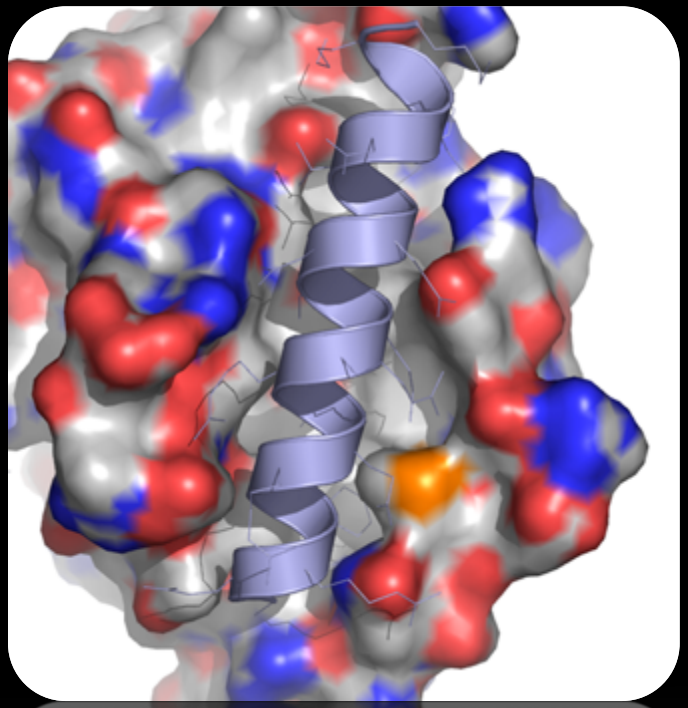
Disease	Oncogene
Lymphoma	BCL2
CLL	
Pancreatic Ca	RAS
Bladder Ca	
Leukemia	
Melanoma	
Prostate Ca	ERG1/ETV1
Many	MYC
Rhabdomyosarcoma	PAX3-FKHR
Synovial Sarcoma	SYT-SSX
Liposarcoma	MDM2

Disease

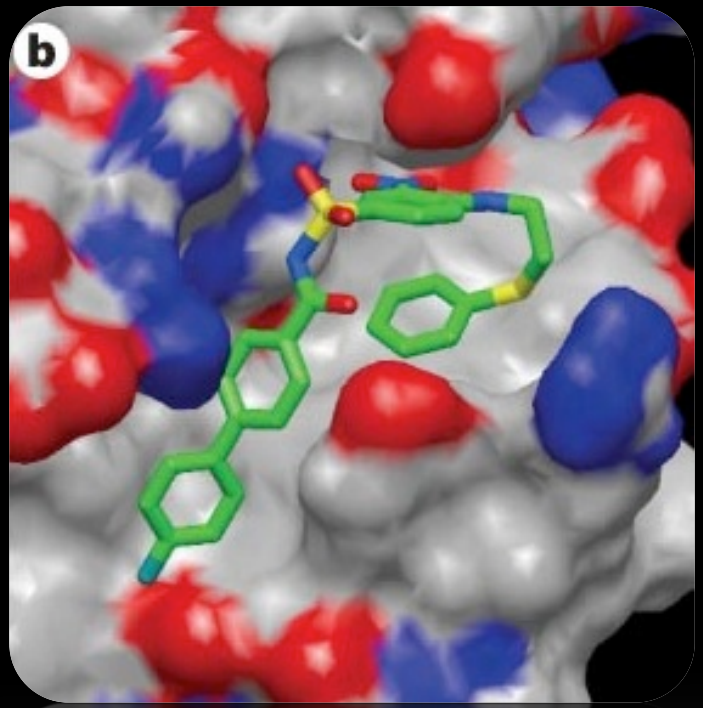
Pathogenesis

Target-based drug discovery

ABT737 – a small molecule BCL2 inhibitor



BH3 peptide bound to BCLxL

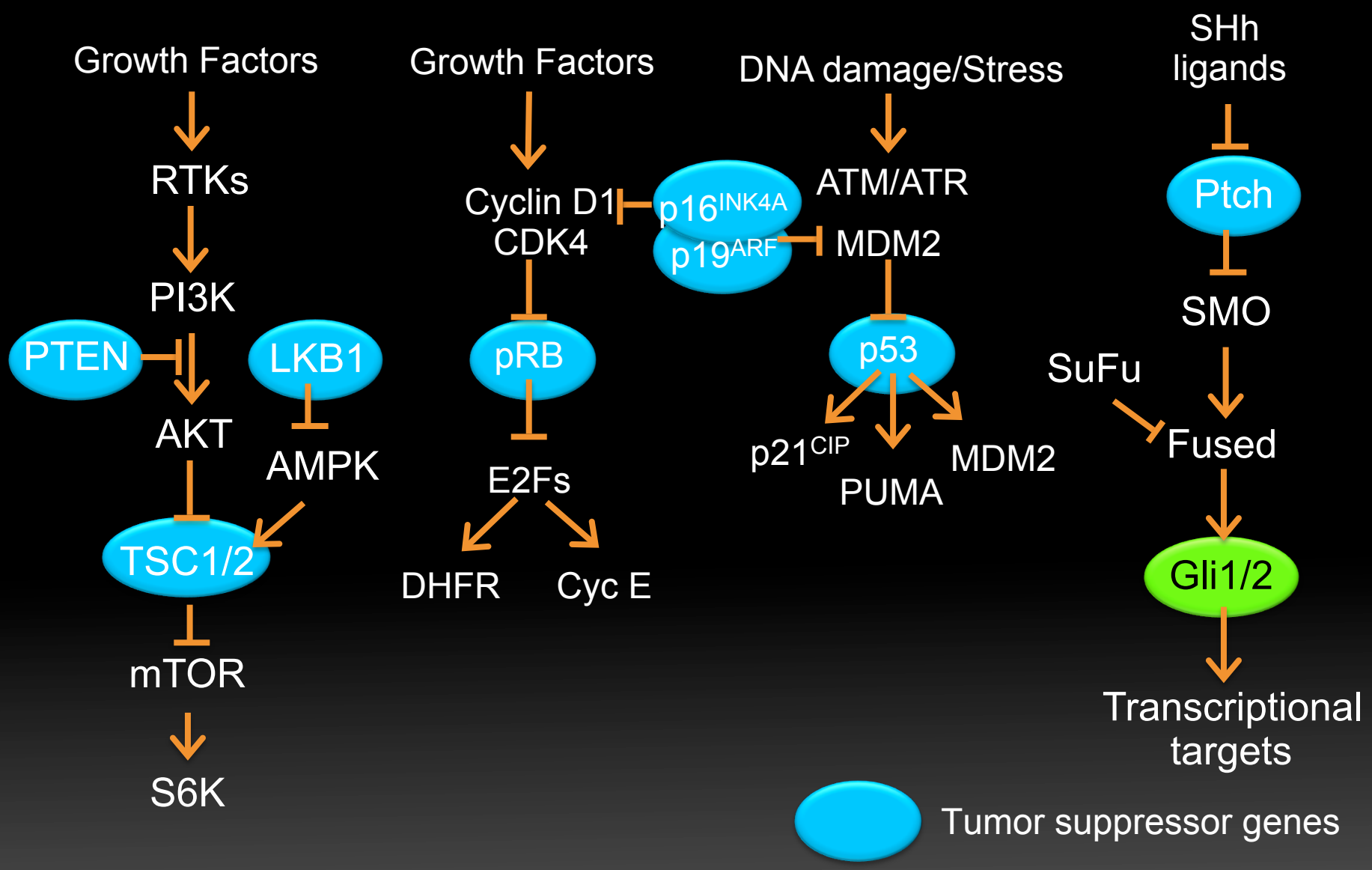


ABT737 bound to BCLxL

- Pre-clinical activity against cell lines bearing the BCL2 translocation.
- ABT-263 – the lead clinical candidate is currently in Phase I/II trials.

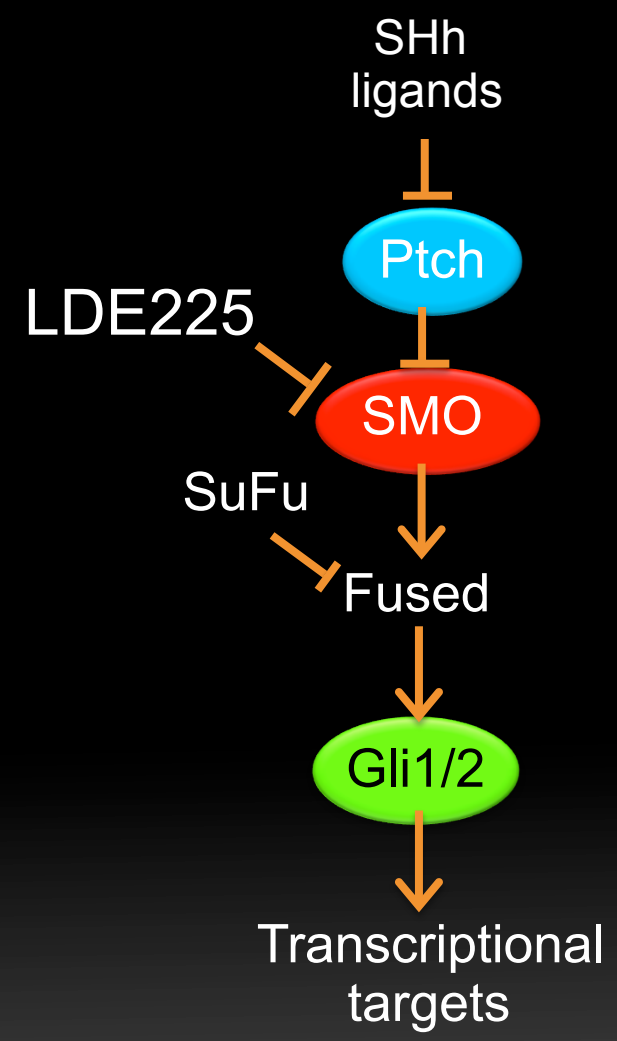
Oltersdorf T et al Nature. 2005 435:677-81.

Problem #2b: Drugging tumor suppressor pathways



Problem #2b: Drugging tumor suppressor pathways

- Germline mutation of PTCH leads to the development of hereditary basal cell carcinoma.
- Acquired mutations in PTCH are found in medulloblastoma (~30%) and in sporadic basal cell carcinoma.
- Cyclopamine discovered as a natural product inhibitor of SMO (Beachy lab).



S. Pan, ACS Med. Chem. Lett. 2010

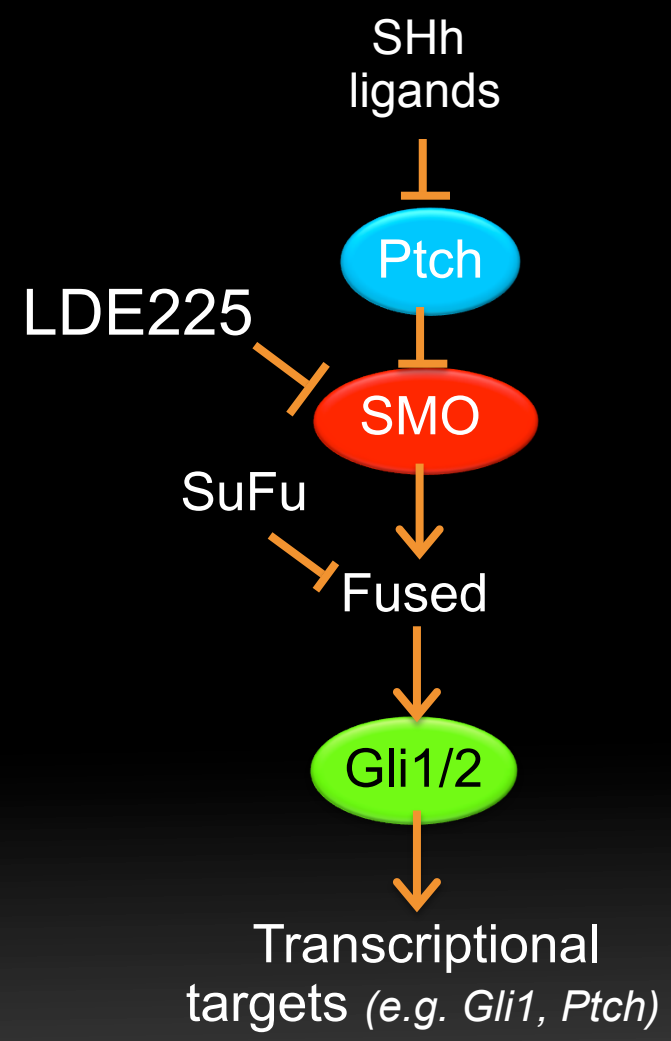
Problem #2b: Drugging tumor suppressor pathways

In vitro Smo binding

Assay	IC_{50} (nM)
Hu Smo	11

Cellular activity

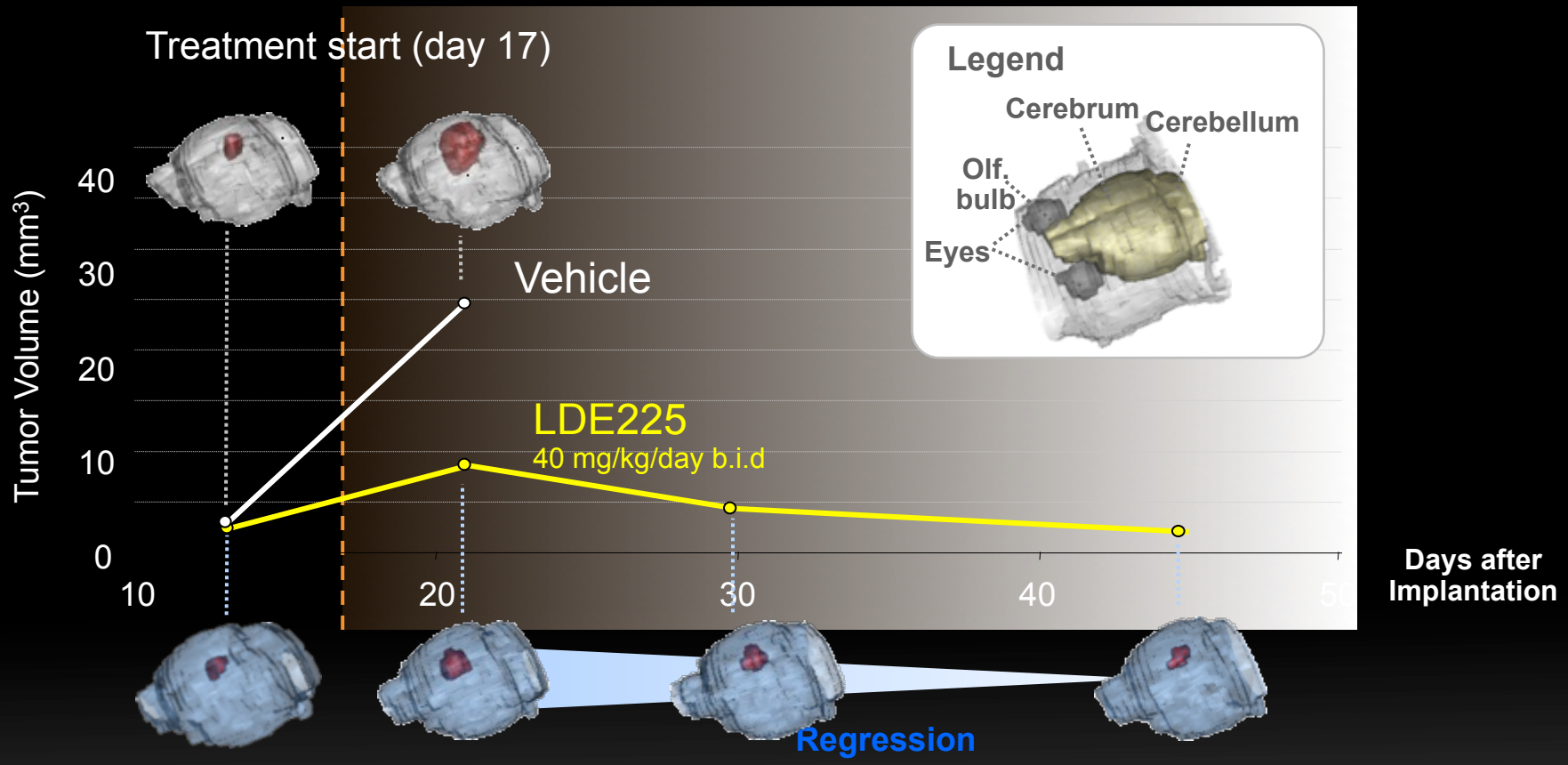
Assay	IC_{50}(nM)
Shh-induced Gli1Luciferase	7
Wnt-induced STF-Luciferase	3900



S. Pan, ACS Med. Chem. Lett. 2010

LDE225activity in orthotopic medulloblastoma

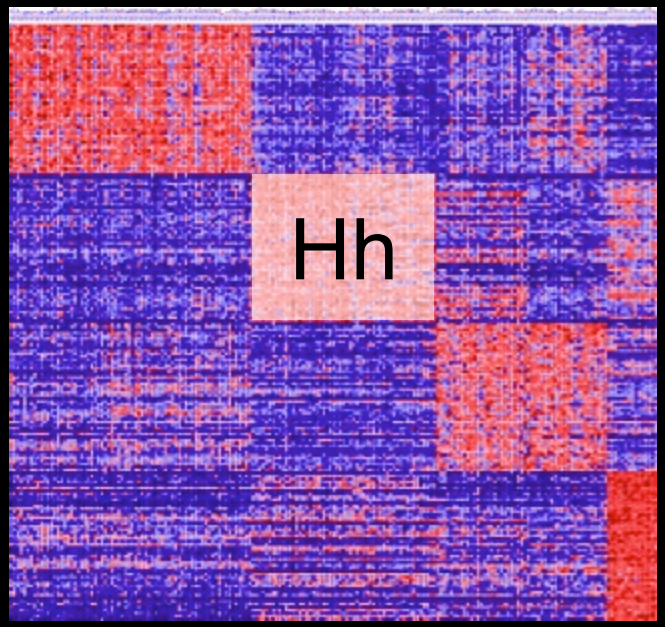
Representative brains from 3D MRI (red indicates tumor)



- In established orthotopic model of medulloblastoma, LDE225 leads to tumor regression up to day 28 from start of treatment.

Jeff Tsao, Juliet Williams

Gene signatures in medulloblastoma



- Medulloblastoma has distinct subsets. ~30% can be defined as "Hh-active" by expression profiles.
- We developed an expression signature using 40 medullo FFPE tumor samples analyzed using TaqMan Low Density Arrays
  - Predictive multi-gene model building using the elastic net method
  - Optimal model selection using 5-fold cross-validation

- More facile than genetic profiling of the pathway.
- Caveat: might include Gli1 amplified tumors (likely resistant to SMO inhibitor).

Geoerger et al. 2012 International Society of Pediatric Oncology. Oral Presentation

LDE225: CR in a child with medulloblastoma

Baseline | Cycle 2 | Cycle 5

Geoerger et al. 2012 International Society of Pediatric Oncology. Oral Presentation

Biomarker signature results – investigational data

Medulloblastoma trial

	Responders/ Hh-activated	Responder/ Hh-non-activated
Adults	3/3 (3 PR)	0/4
Pediatrics	2/2 (2 CR)	0/12
Total	**5/5**	**0/16**

Geoerger et al. 2012 International Society of Pediatric Oncology. Oral Presentation

Synthetic lethality in cancer therapeutics

Synthetic Lethality

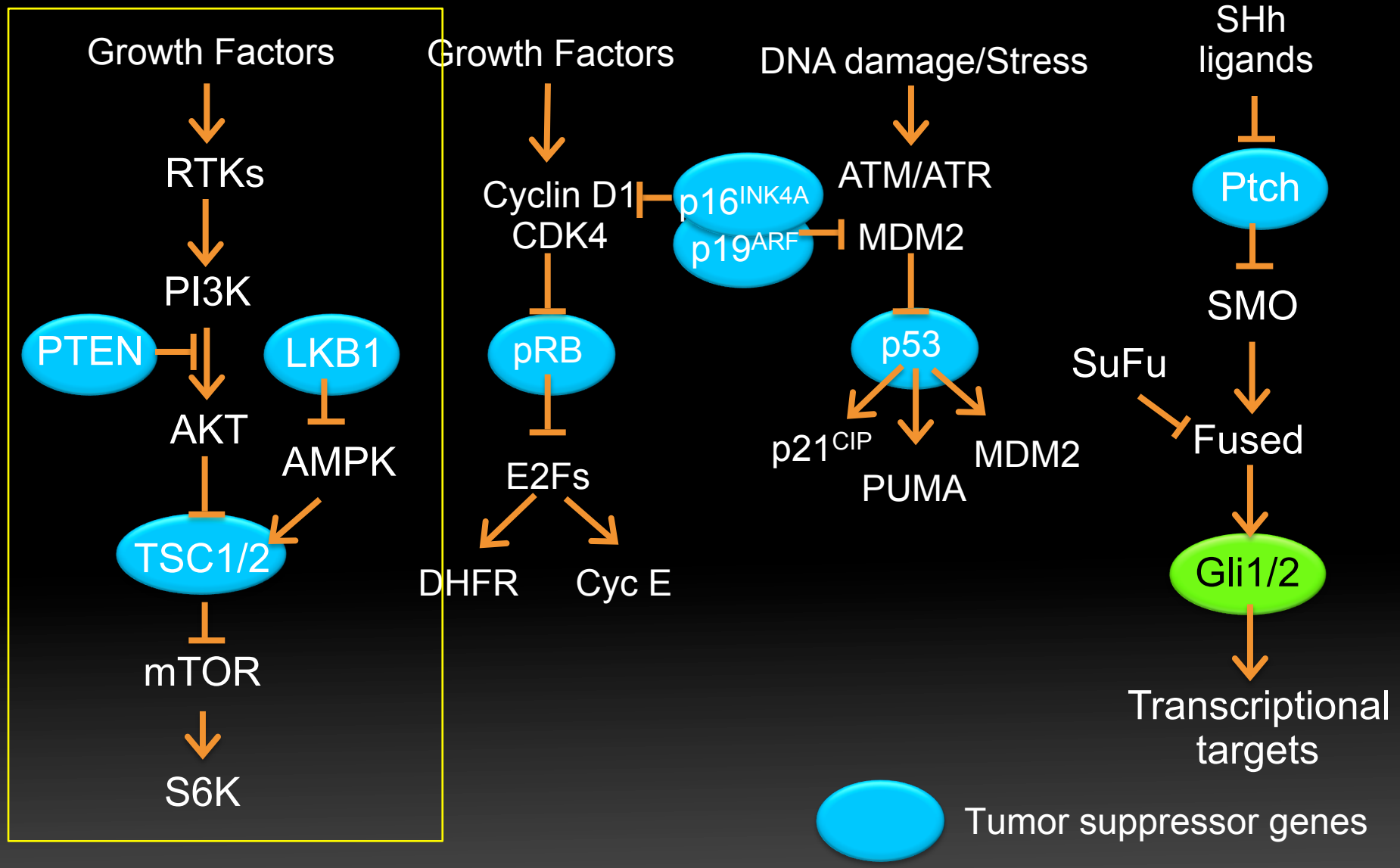
Genetic event	Phenotype
A	Viable
B	Viable
A & B	Lethal

Synthetic Lethality

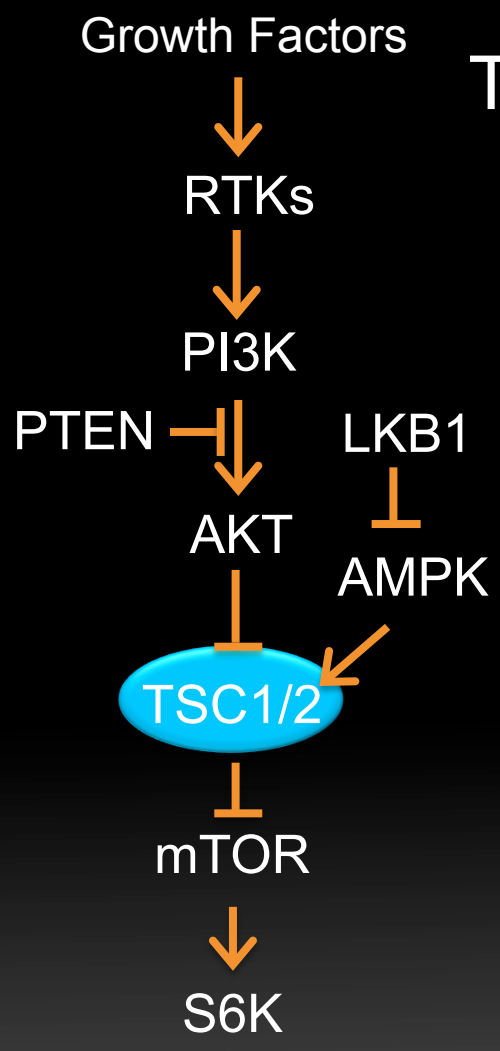
Genetic event	Phenotype
PTCH	Viable
LDE225	Viable
PTCH & LDE225	Lethal

Major advantage: Hypothesis driven clinical trials.

Problem #2b: Drugging tumor suppressor pathways



Tuberous sclerosis and mTOR inhibition



Tuberous Sclerosis

- 1-2 million patients worldwide
- Recessive mutations in TSC1/2

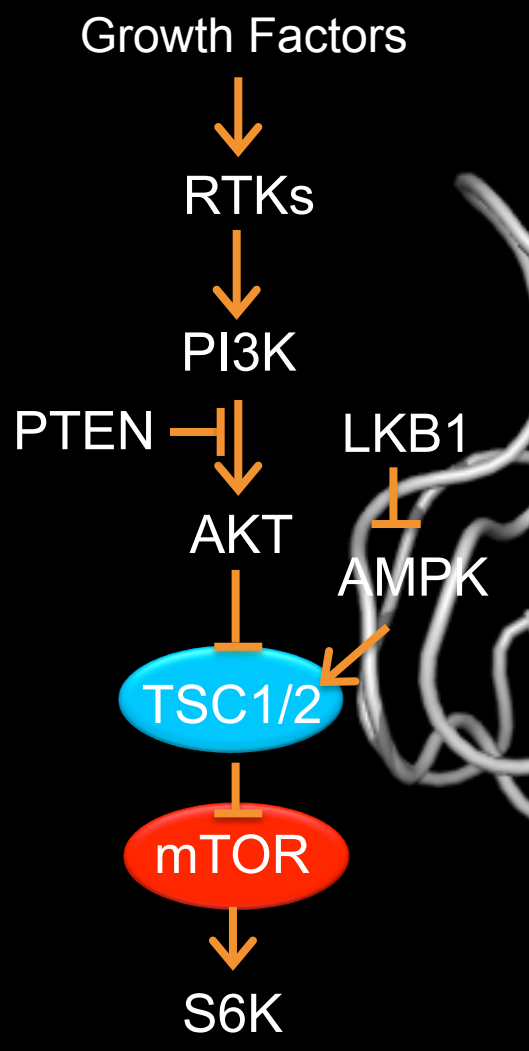
Manifestations:

Renal: angiomyolipomas

CNS: cortical tubers, subependymal giant astrocytomas, seizures (60-90%)

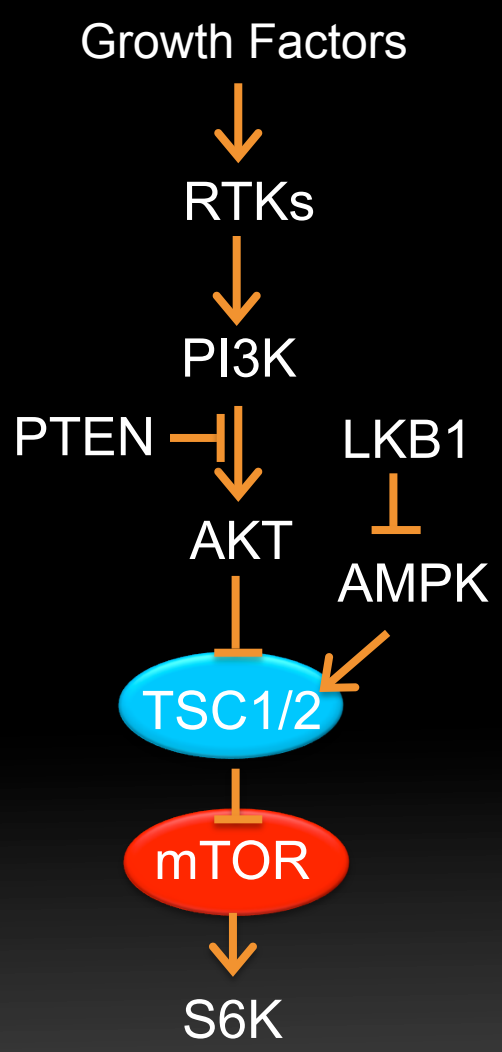
Skin: subungual fibromas, facial angiofibromas, hypomelanoytic plaques

RAD001: an allosteric mTORC1 inhibitor

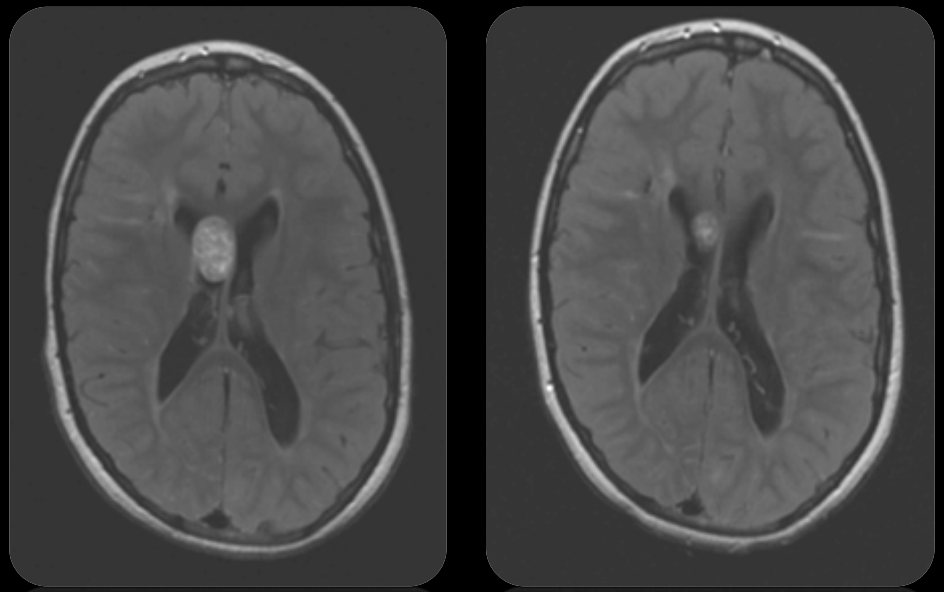


RAD001 (Everolimus) – bound to FKBP12

RAD001: an allosteric mTORC1 inhibitor



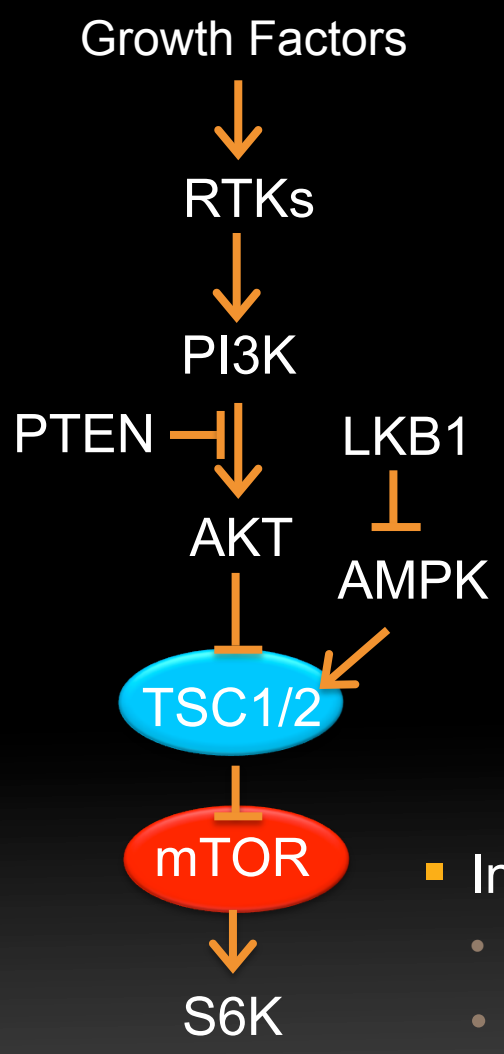
Subependymal Giant Cell Astrocytoma

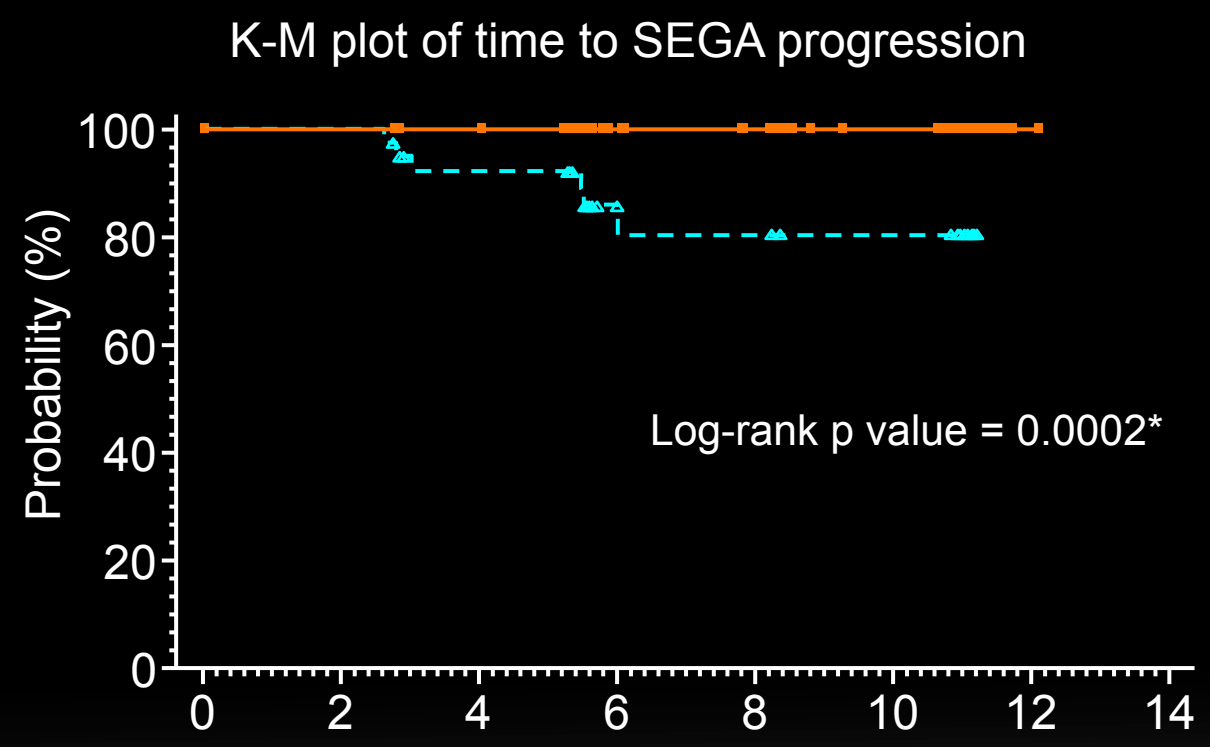


Pre-treatment RAD001

D. Franz, J. Bissler (Univ. Of Cinncinnati)

RAD001: an allosteric mTORC1 inhibitor





- In Phase III Exist-I trial:
  - 35% partial response rate in treated vs. 0% in placebo
  - In the AML renal tumors 53% PR rate v 0% in placebo.

M. Bebin et al ECCO-ESMO 2011

Synthetic lethality in cancer therapeutics

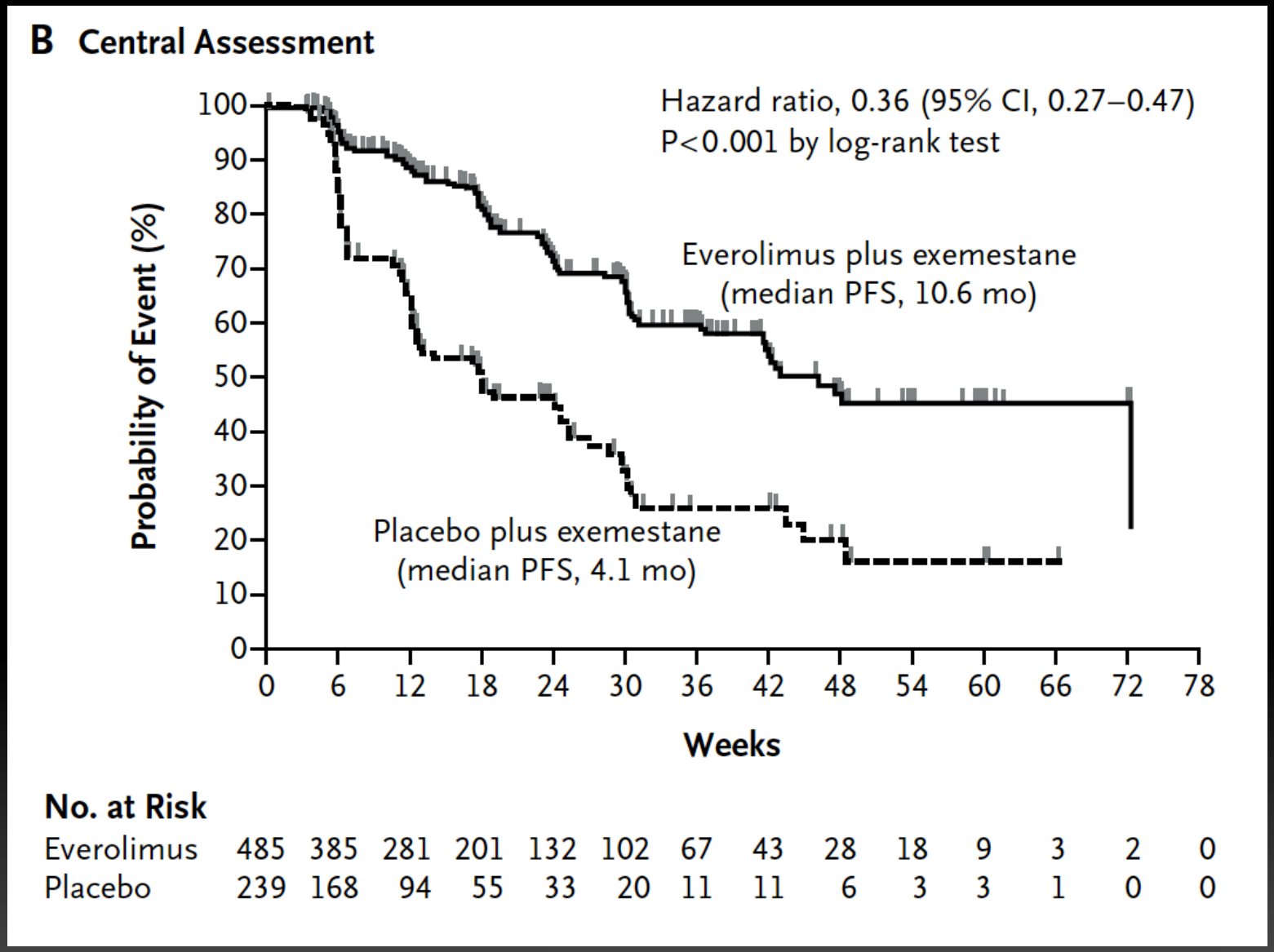
Synthetic Lethality

Genetic event	Phenotype
A	Viable
B	Viable
A and B	Lethal

Synthetic Lethality

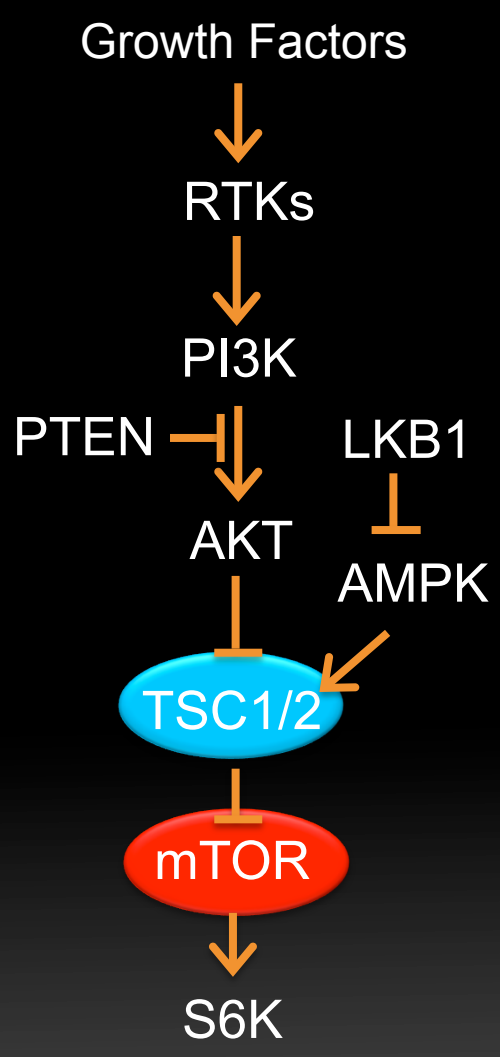
Genetic event	Phenotype
TSC	Viable
RAD001	Viable
TSC + RAD001	Lethal

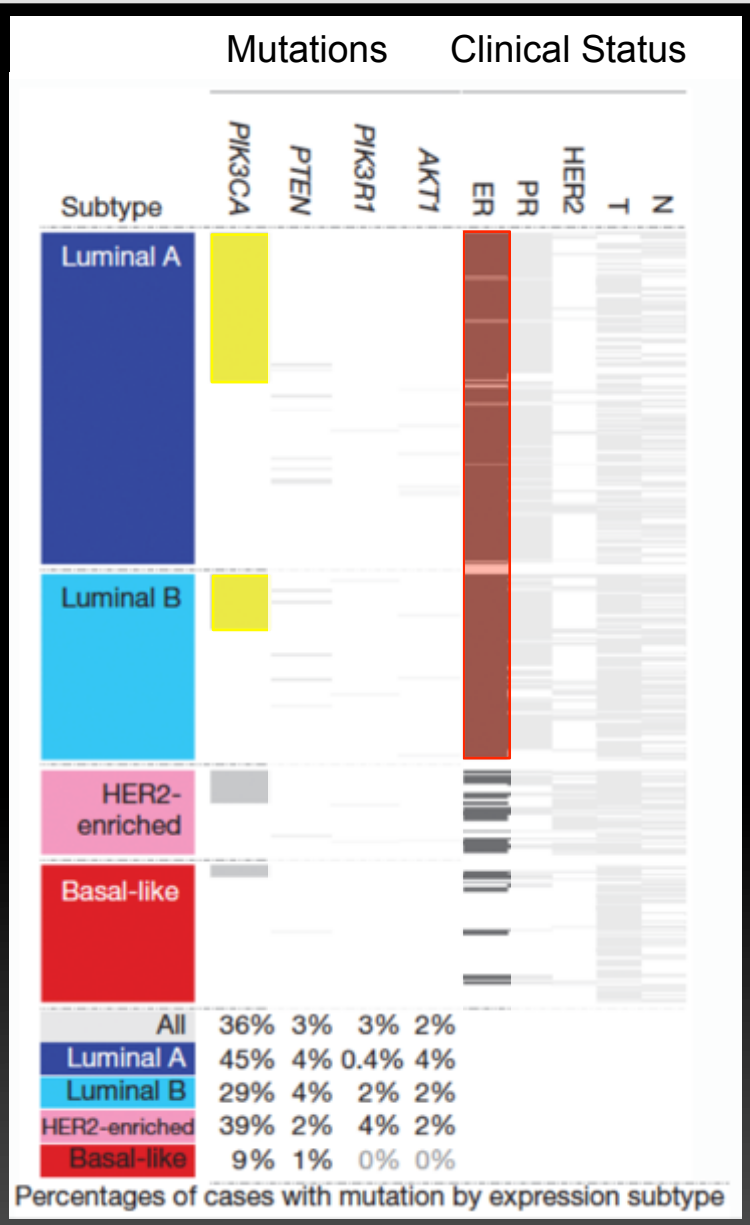
Everolimus: approved in ER+ breast cancer



Baselga et al 2012 N Engl J Med 366;6

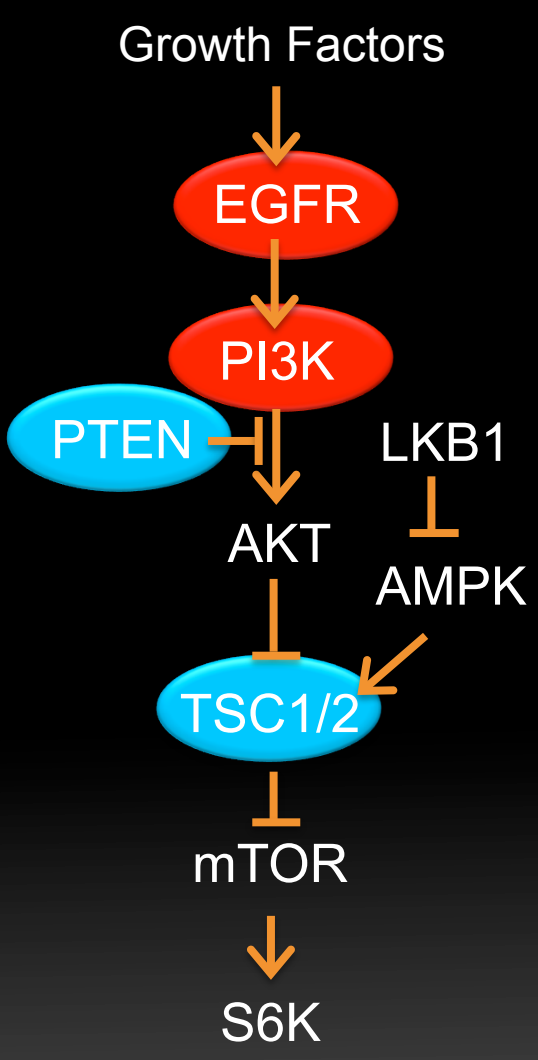
Is there an underlying genetic linkage in breast cancer?

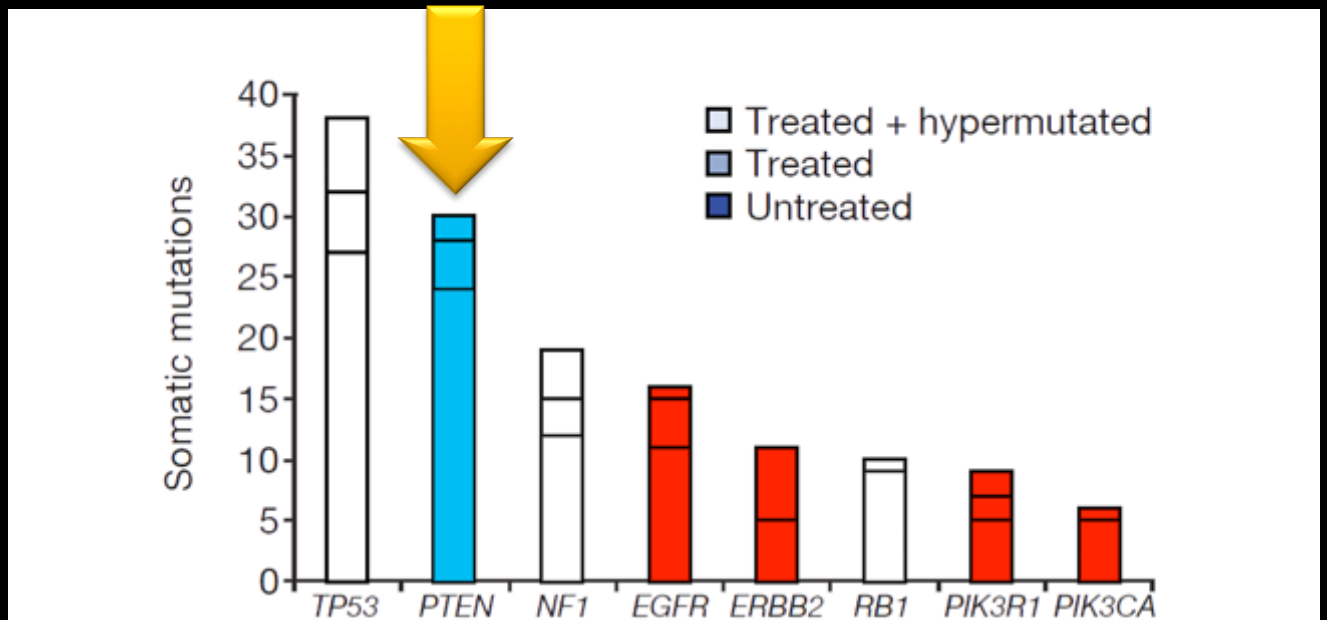




*The Cancer Genome Atlas Network, Nature 2012 (*modified Figure 1)*

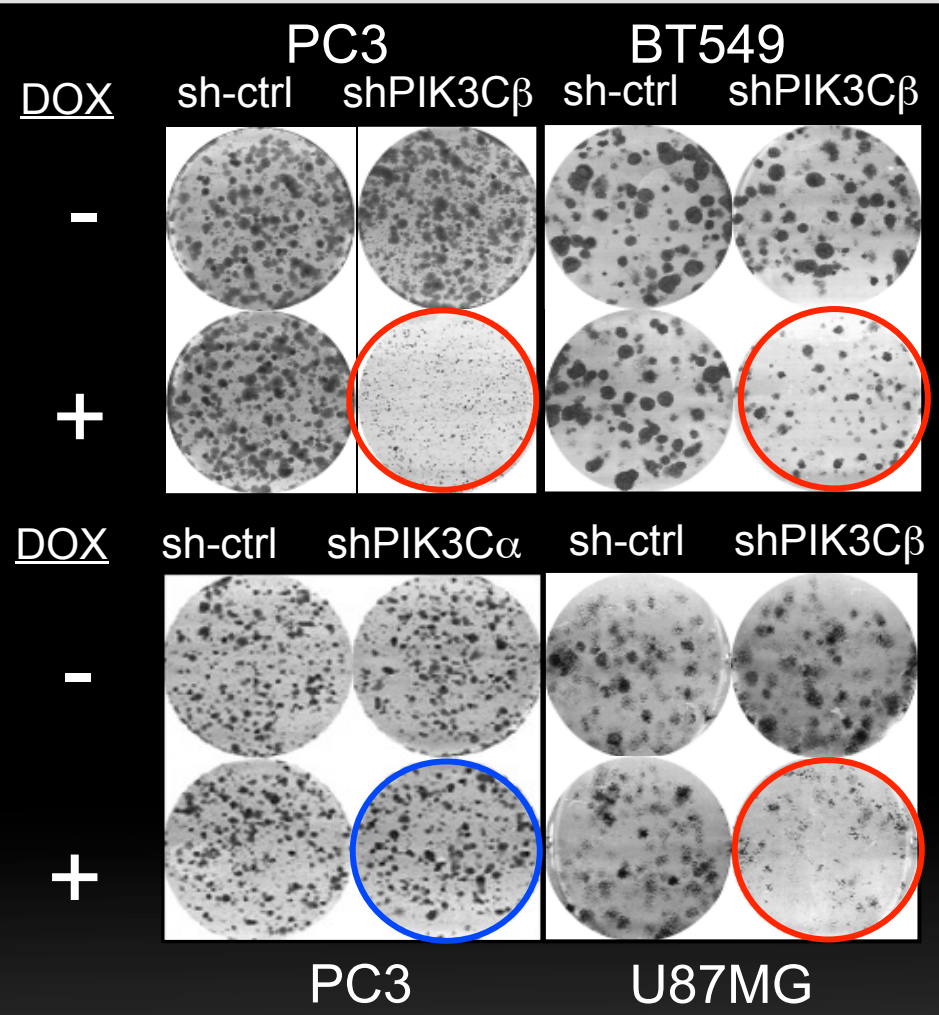
PI3K pathway – genetic alterations in glioma

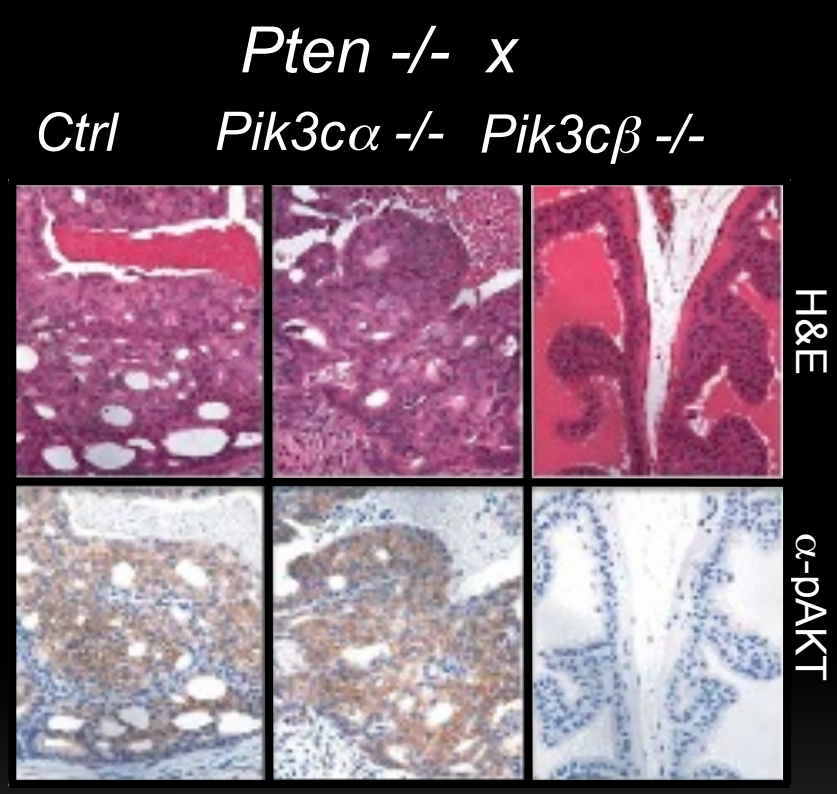




Nature. 2008 Oct 23;455(7216):1061-8. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Cancer Genome Atlas Research Network.

PTEN loss leads to PI3Kβ dependence

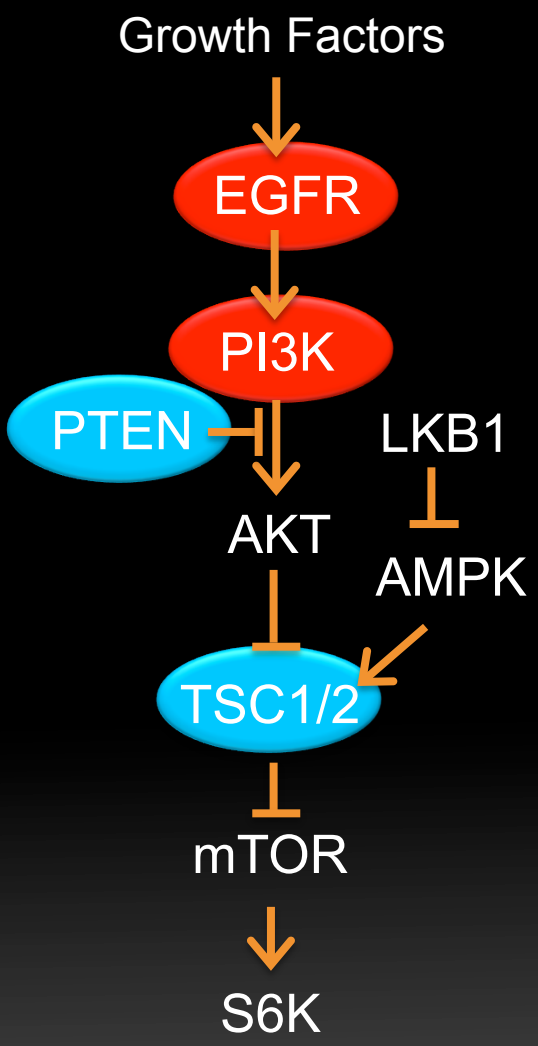


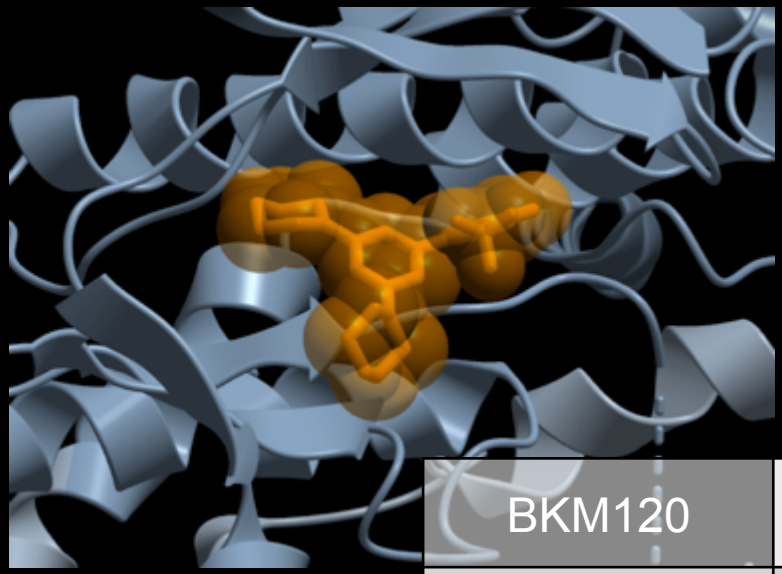


- Inducible knockdown of p110α blocks PTEN-deficient cell growth in vitro
- Constitutive KO of shPIK3Cβ in mice blocks prostate tumor formation in PTEN-/-.

Susan Wee, D. Weiderschain et al, PNAS 2008
Shidong Jia et al, Nature 2008

BKM120: a pan-Type I PI3K inhibitor

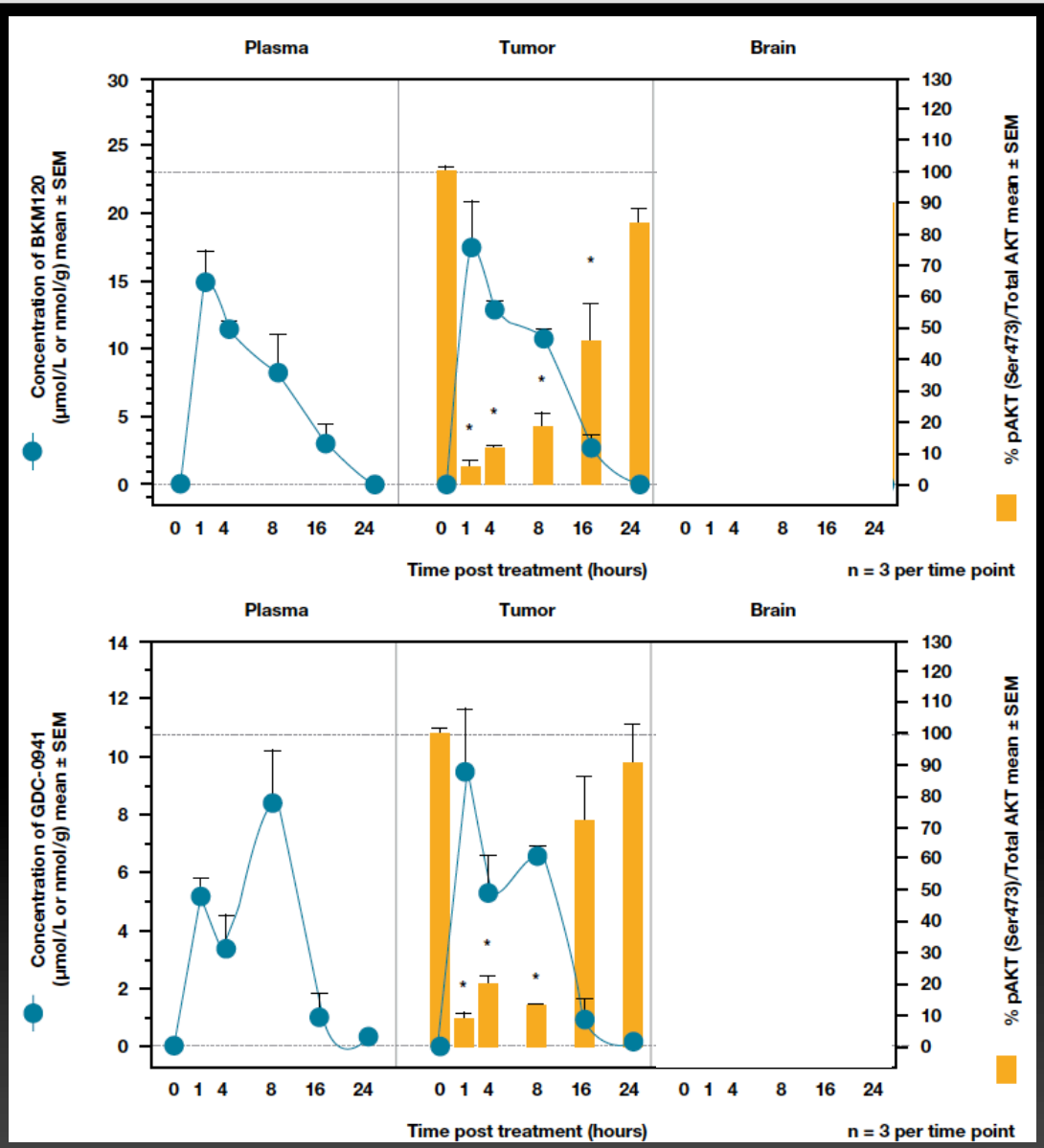


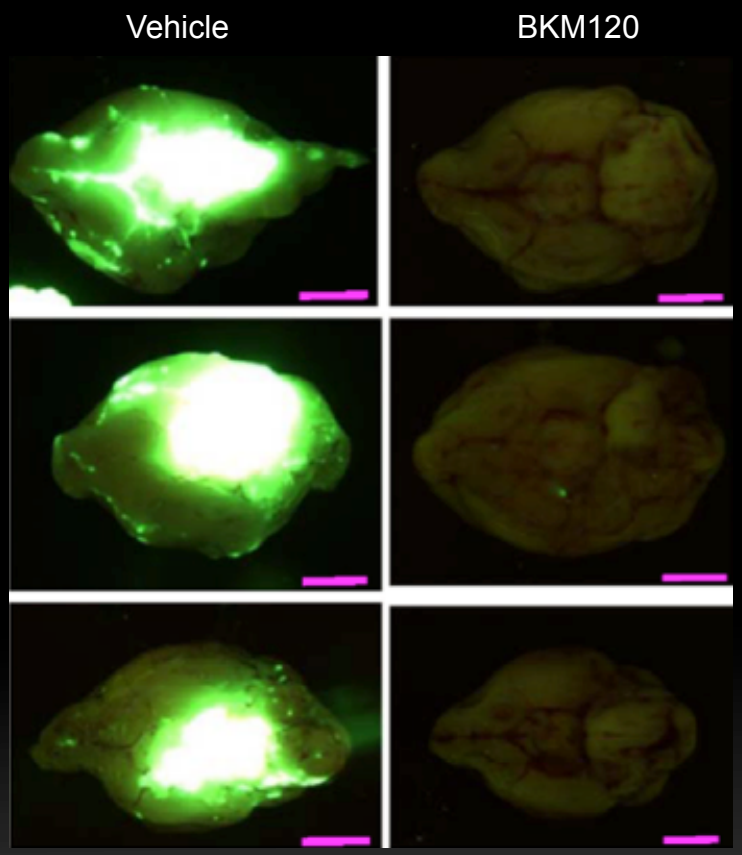


BKM120	In vitro IC_{50} nM	Cellular IC_{50} nM
p110α wt	52	93
p110α H1047R	58	
p110α E542K	84	
p110α E545K	99	
p110β	166	101
p110δ	116	
p110γ	262	242
VPS34	2410	

Maira SM Pecchi S et al Mol Cancer Ther. 2012

BKM120 – tumor vs. brain PK/PD





Brain – EGFP-labeled MBA-MB-453 cells

Nanni P et al PLoS One. 2012;7(6):e39626.

BKM120 undergoing investigational trials in GBM

- Novartis is currently conducting 2 clinical trials exploring the safety and activity of BKM120 in GBM
- Phase I study of BKM120 in combination with temozolomide and Radiation therapy for patients with newly diagnosed GBM: this trial is currently recruiting patients at multiple clinical centers in the US, Europe, and Australia; initial dose cohorts have been enrolled and no unexpected safety signals have been encountered.
- Phase II study of single agent BKM120 for patients with recurrent GBM: currently ongoing with robust enrollment at multiple centers in the US;
  - In arm 1, the activity of BKM120 at a biomarker (PK/PD) level will be evaluated where patients receive BKM120 for 2 weeks and then undergo surgery before continuing BKM120 – tissue will be analyzed at the end of the trial
  - In arm 2, patients with recurrent GBM with PI3K pathway activation are being enrolled to assess the efficacy of BKM120 – progression free survival is the primary endpoint

Synthetic lethality in cancer therapeutics

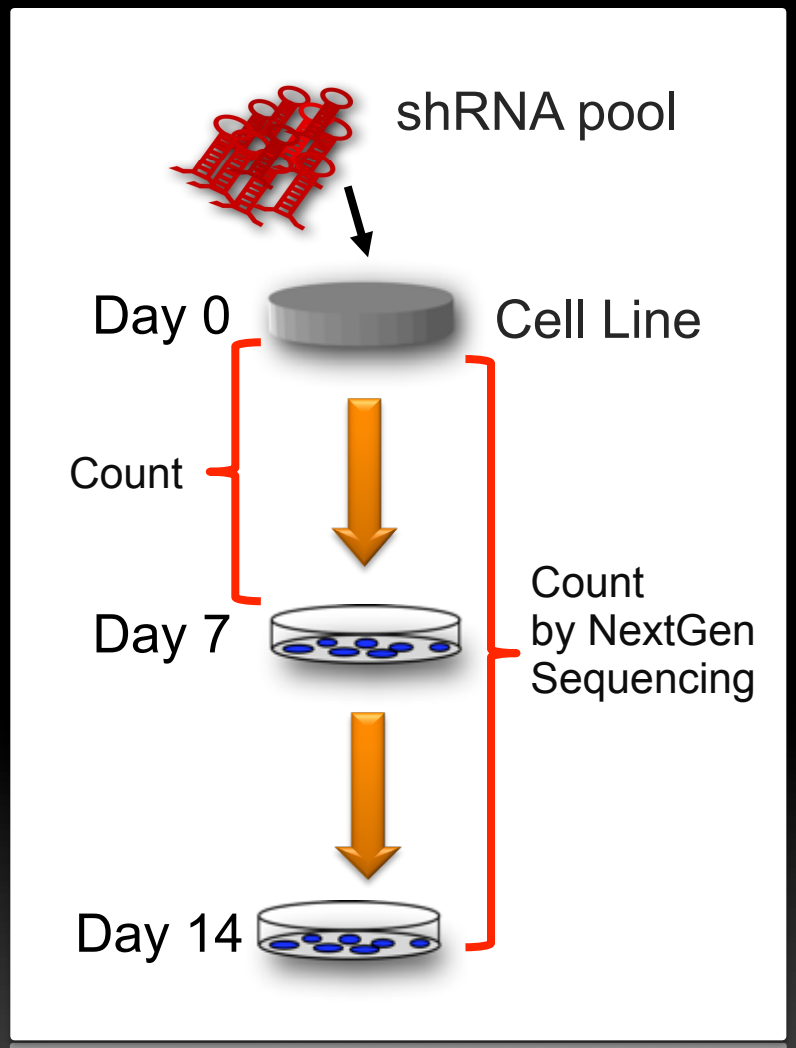
Synthetic Lethality

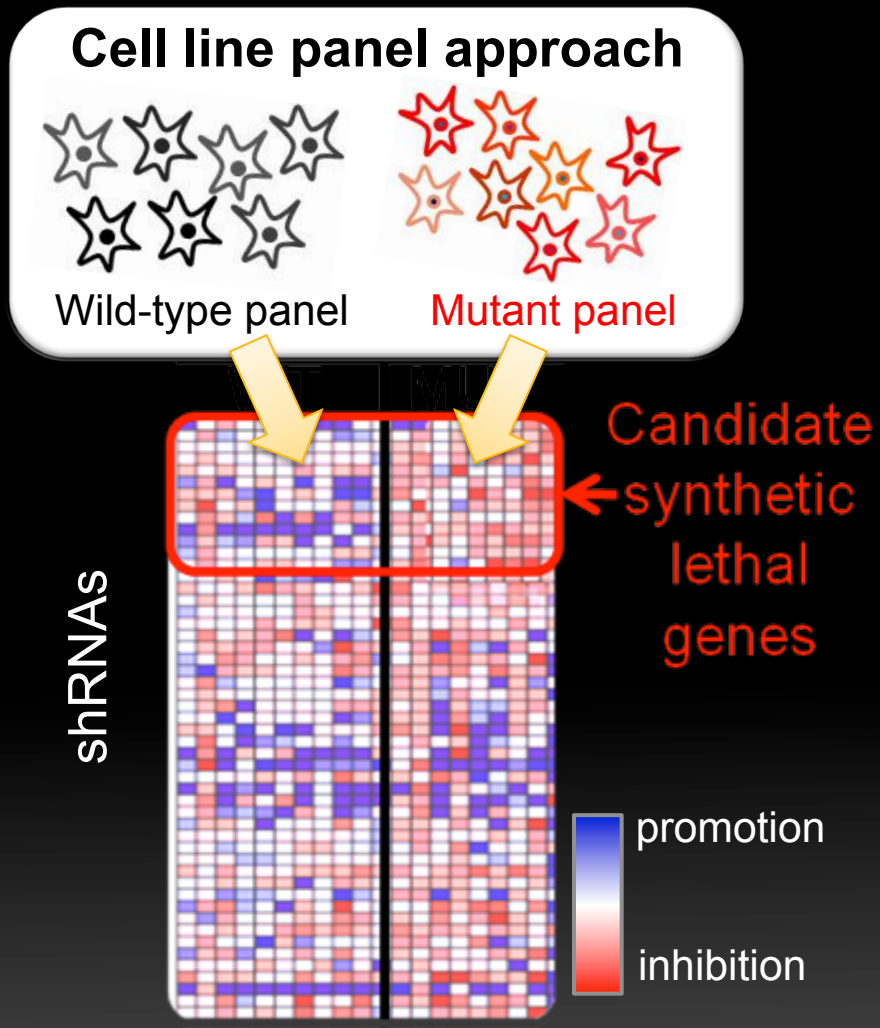
Genetic event	Phenotype
A	Viable
B	Viable
A and B	Lethal

Synthetic Lethality

Genetic event	Phenotype
PTEN	Viable
BKM120	Viable
PTEN + BKM120	Lethal

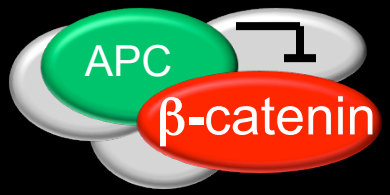
Finding "synthetic" lethality thru shRNA screening



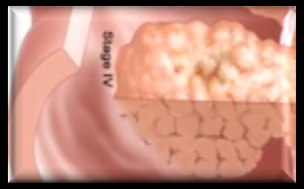


Pooled shRNA screen identifies β-catenin dependence of WNT pathway mutated cancer cell lines

APC/β-catenin pathway in cancer

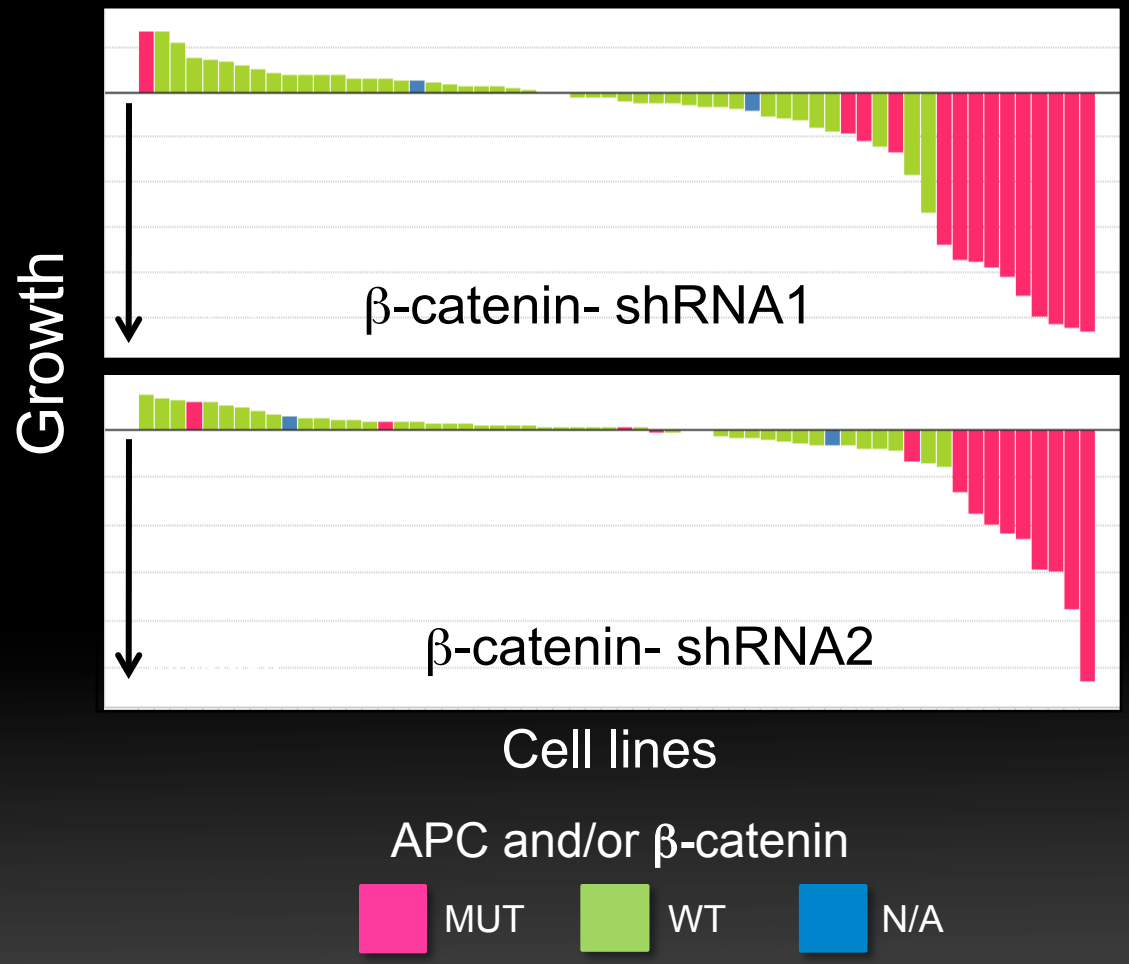


Colorectal & other cancer



Top 5 selectively lethal shRNAs In *APC/β-cat* mutant cells

shRNA	p value
β-catenin-426	1.15E-15
β-catenin-2202	1.31E-10
Hit #1	8.32E-07
β-catenin-2279	4.73E-06
Hit #2	9.40E-06



Two models of drug development

What are the problems or impediments to Plan B?

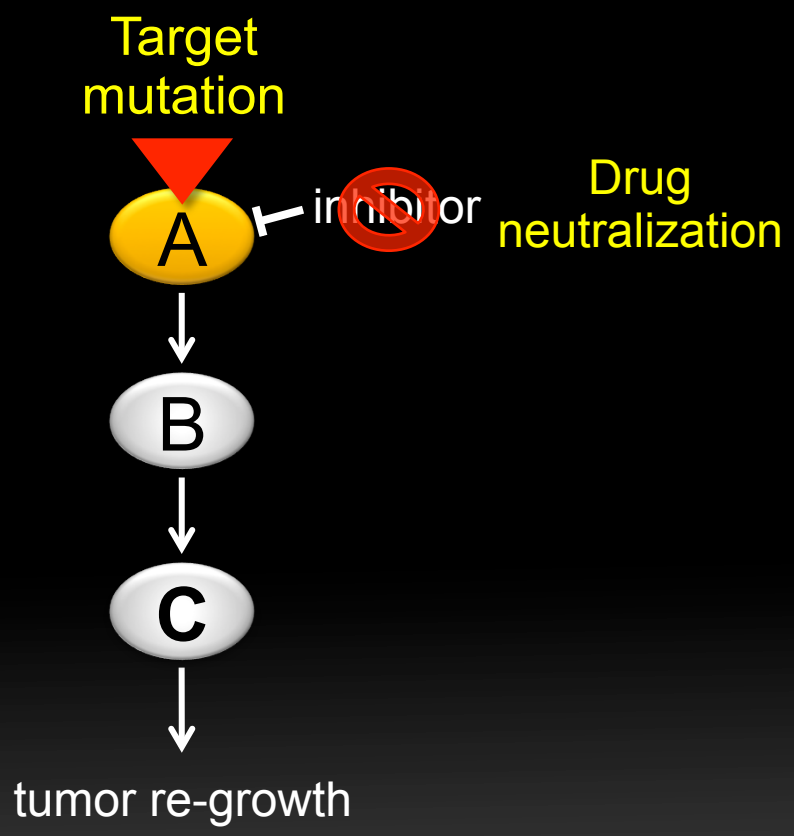
#1. We do not know the complete compendium of genetic alterations in cancer.

#2. Most known genetic alterations have not led directly to a drug candidate.

#3. Resistance develops to targeted agents.

Mechanisms of resistance

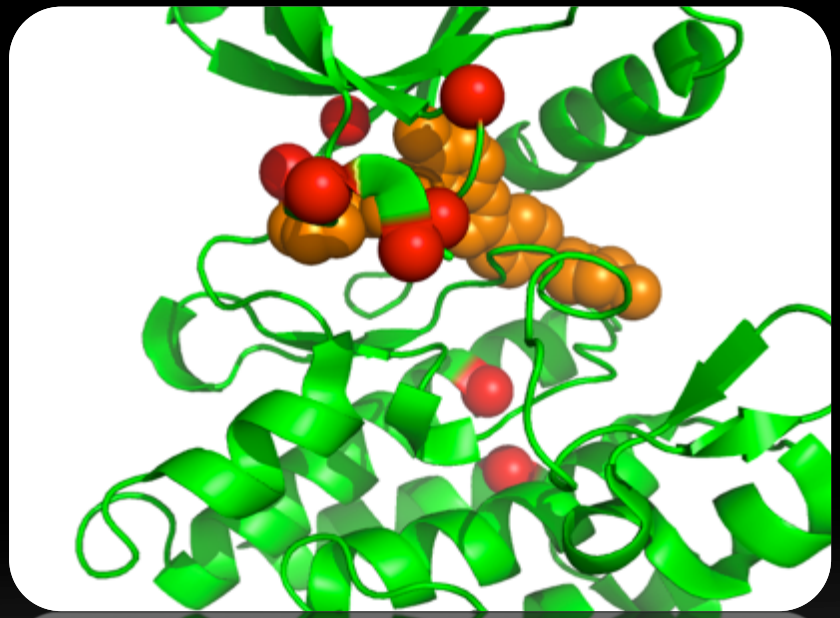
Mechanisms that antagonize target inhibition

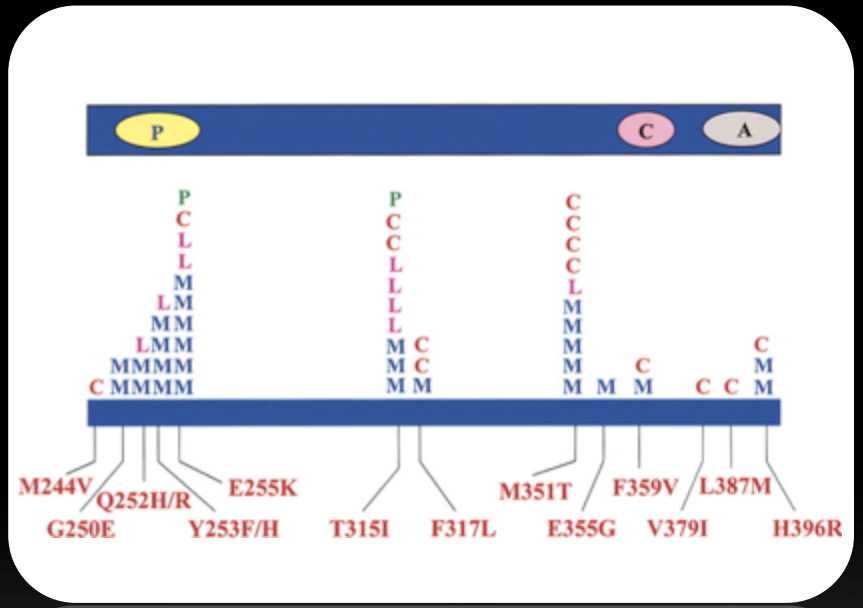


Addicting Oncogene and Drug Target

Resistance to BCR-ABL inhibition

Mutations leading to insensitivity/resistance to imatinib





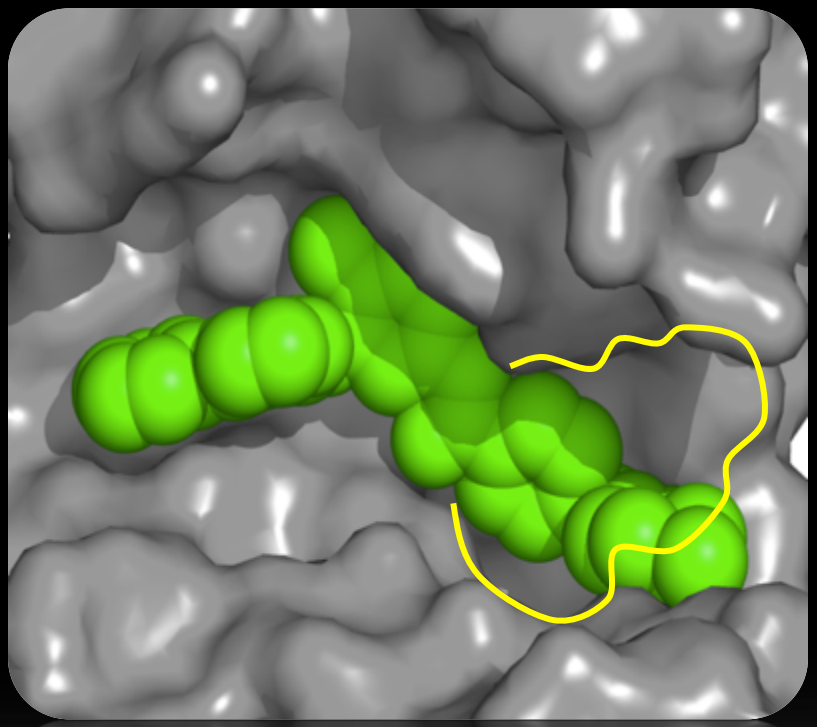
Pathway Reactivation
Disease Progression

Azam M et al. Cell 2003

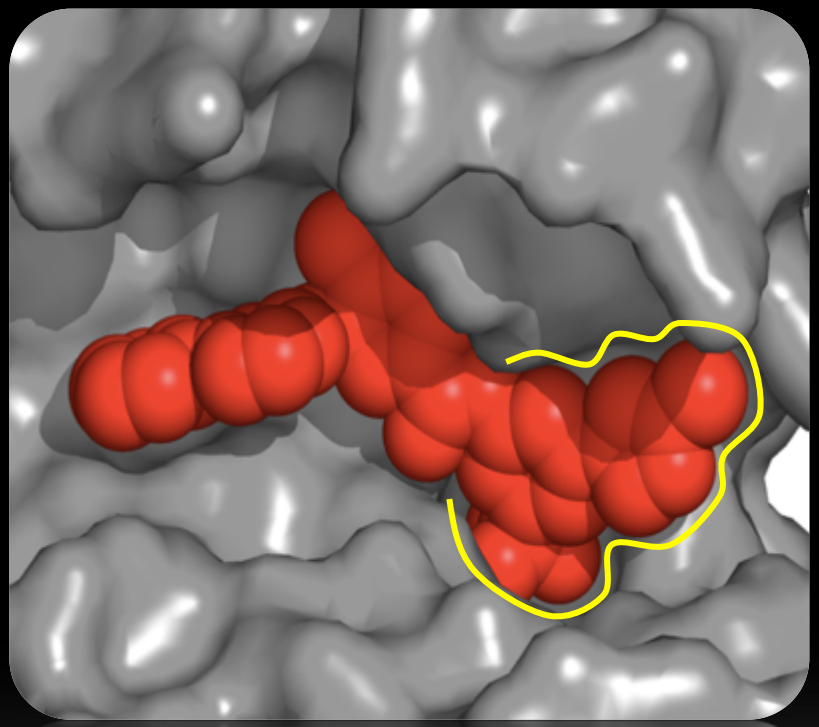
Shah N et al. Cancer Cell. 2002

Resistance to BCR-ABL inhibition

Imatinib (Gleevec™)



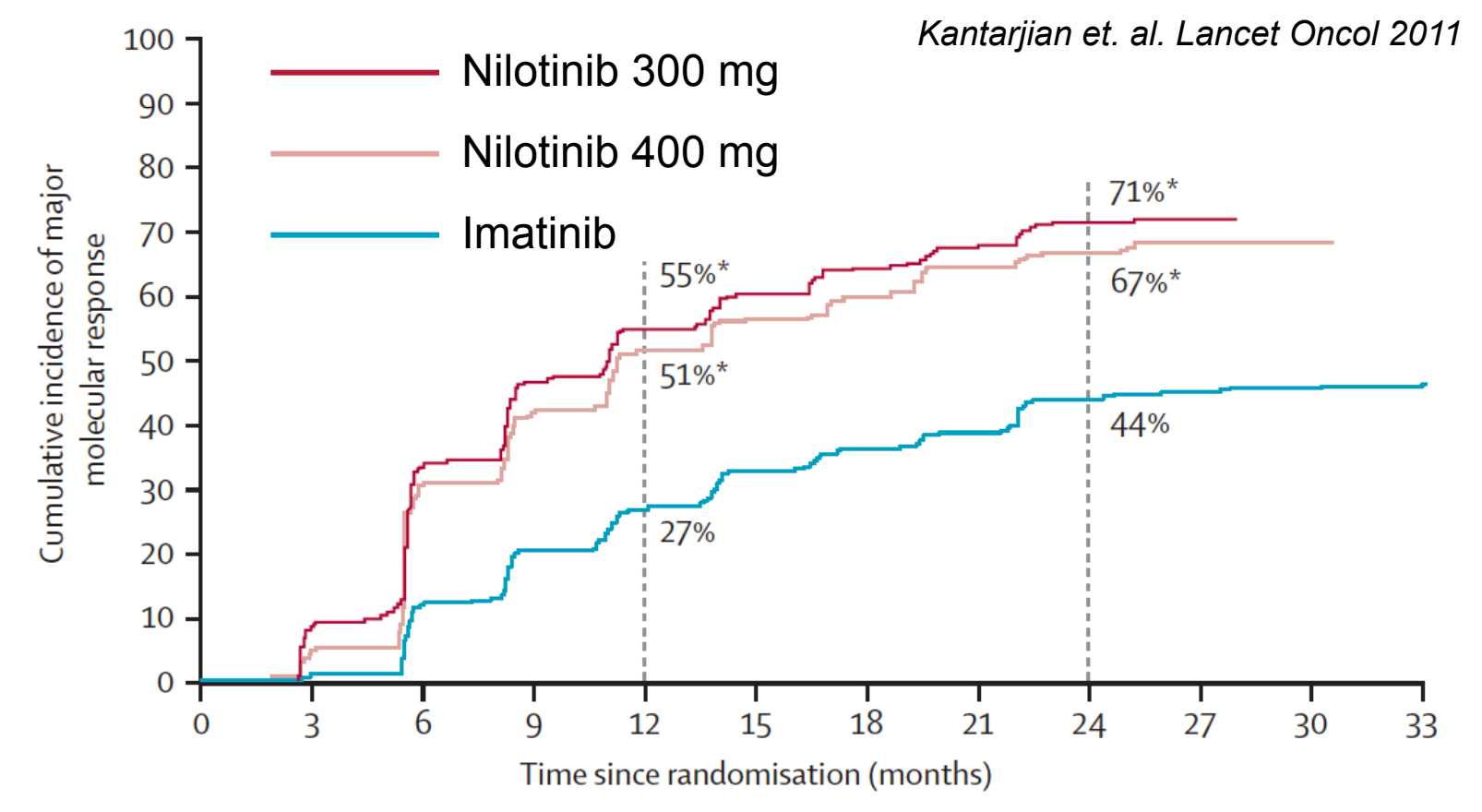
Nilotinib (Tasigna™)



Feature	Imatinib	Nilotinib
BCR-ABL Inhibition (cell IC_{50})	221 nm →	20 nm
cKIT inhibition (cell IC_{50})	108 nM →	151 nM

Weisberg E, Manley PW et al Cancer Cell. 2005 7:129-41

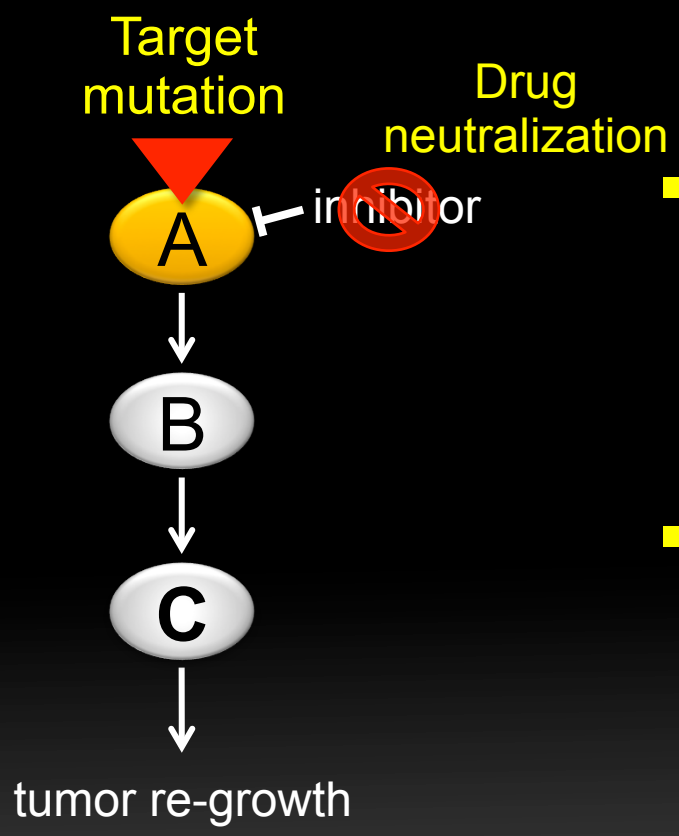
Improved BCR-ABL inhibition improves outcomes



Feature	Imatinib	Nilotinib
BCR-ABL Inhibition (cell IC_{50})	221 nm →	20 nm
cKIT inhibition (cell IC_{50})	108 nM →	151 nM

Mechanisms of resistance

Mechanisms that antagonize target inhibition



- In some cases, improved or enhanced targeted inhibition can overcome resistance
- Such improved inhibitors will likely have improved efficacy in the front-line setting.
- Question: Are there other opportunities?

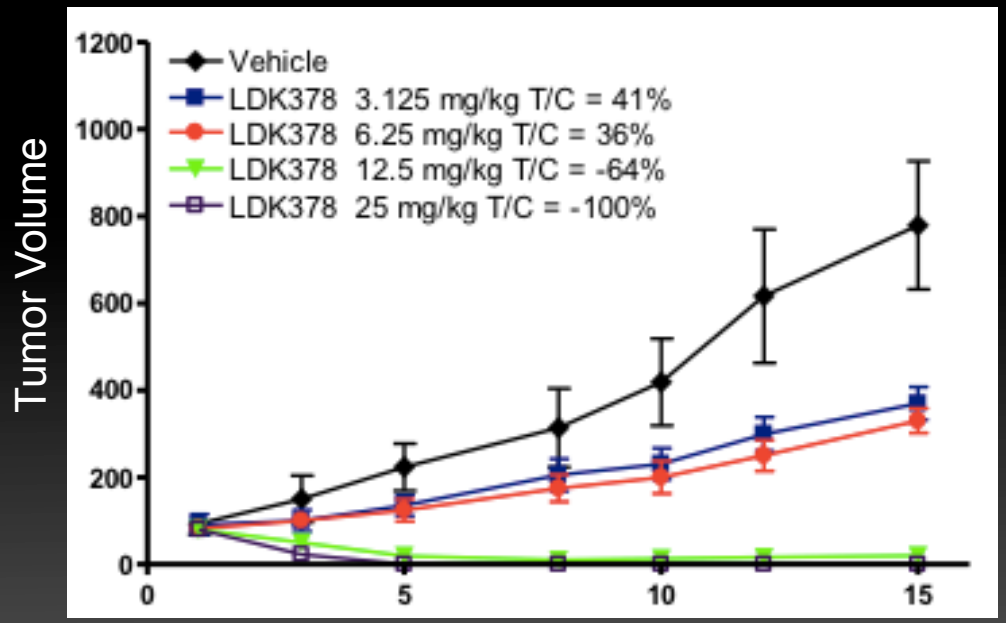
A Addicting Oncogene and Drug Target

LDK378 – a potent ALK inhibitor

Genomics Institute of the Novartis Research Foundation

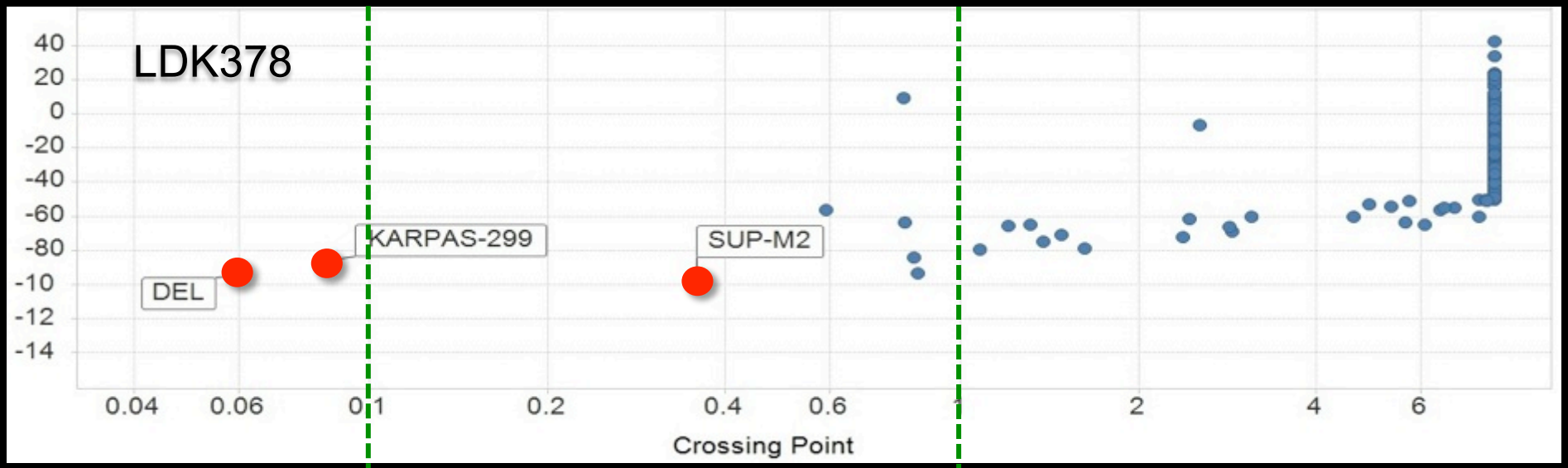
- ALK-driven lung cancers have high response rate to Crizotinib.
- However, resistance does develop readily.
- Question: will a more potent ALK inhibitor work in the Crizotinib refractory setting (akin to Nilotinib)

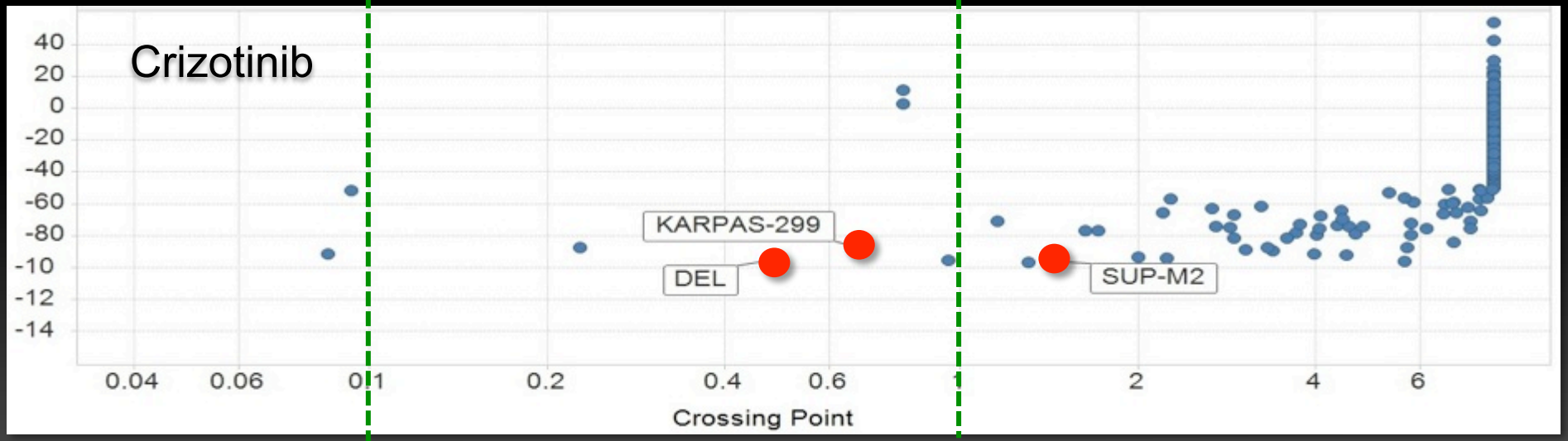
Assay		Crizotinib IC_{50} (μM)
Enzymatic		
ALK		0.003
MET		0.008
Cell-based		
ALK		0.11
MET		0.028



Pierre-Yves Michellys Nanxin Li

Comparing inhibitors in the Cancer Cell Line Encyclopedia (CCLE) *2012 profiling data*

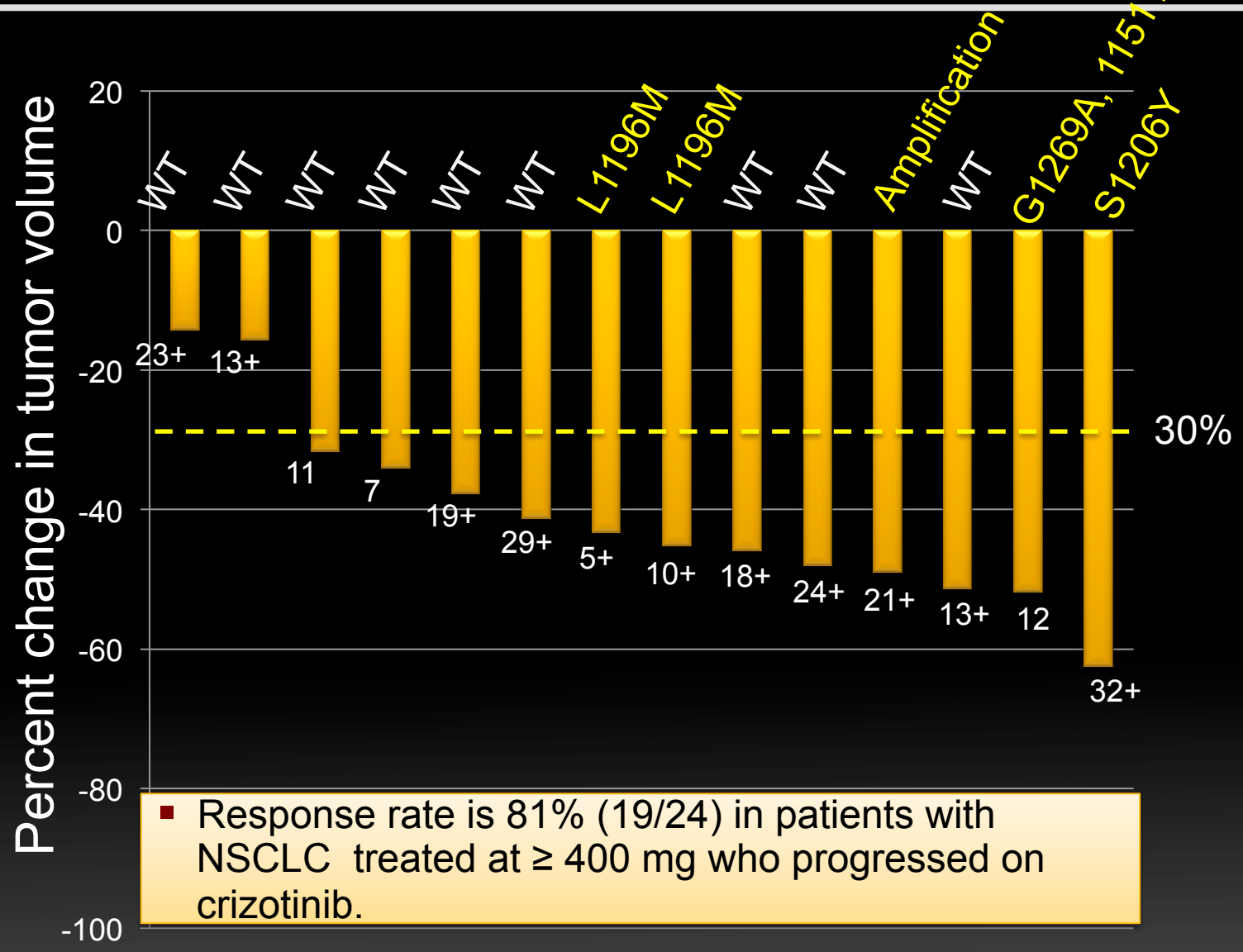




0.1 μM

1.0 μM

LDK378: Efficacy in ALK+ TKI-Resistant NSCLC



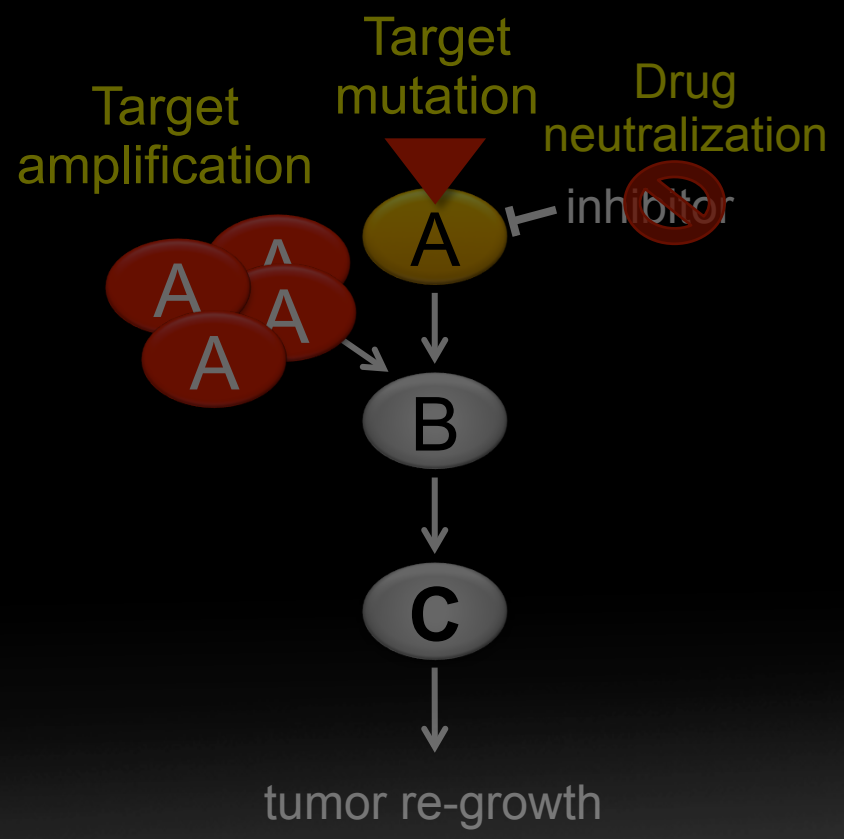
- Response rate is 81% (19/24) in patients with NSCLC treated at ≥ 400 mg who progressed on crizotinib.

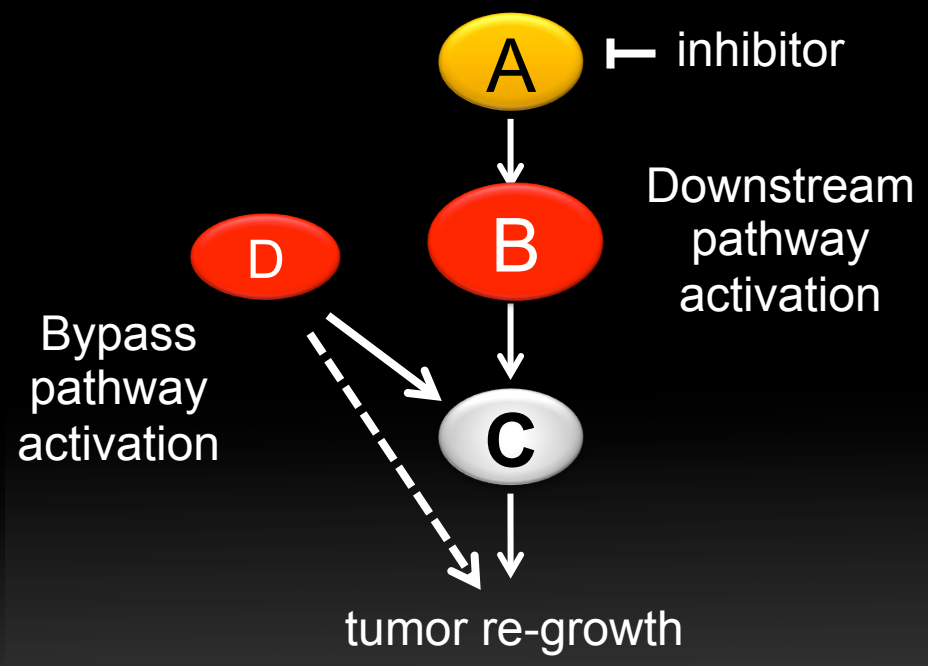
R. Mehra, A. Boral, A. Shaw ASCO 2012

Mechanisms of resistance in the BRAF setting

Mechanisms that antagonize target inhibition

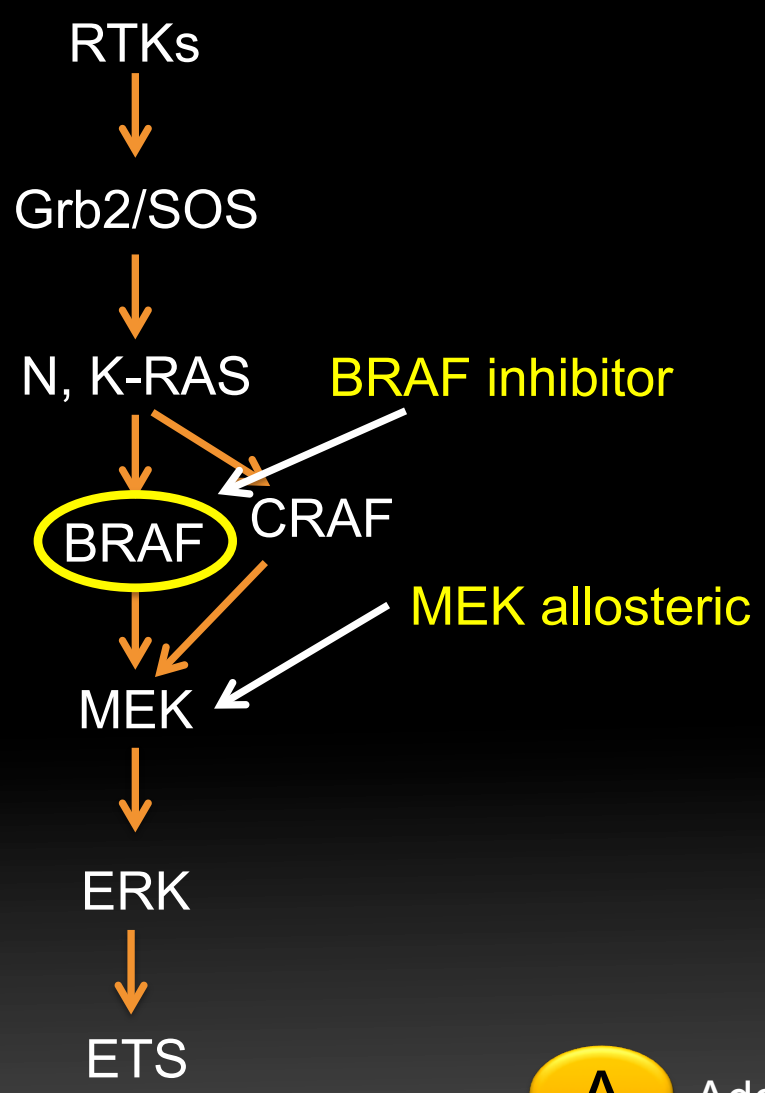
Mechanisms that bypass target dependence



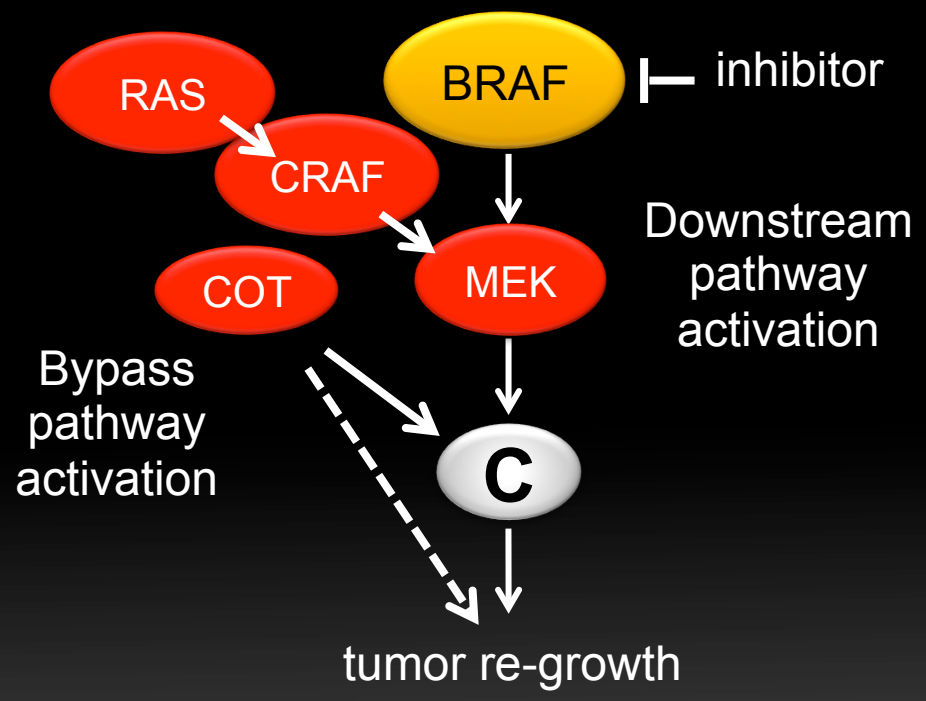


A Addicting Oncogene and Drug Target

Mechanisms of resistance in the BRAF setting



Mechanisms that bypass target dependence



A Addicting Oncogene and Drug Target

Two models of drug development

What are the problems or impediments to Plan B?

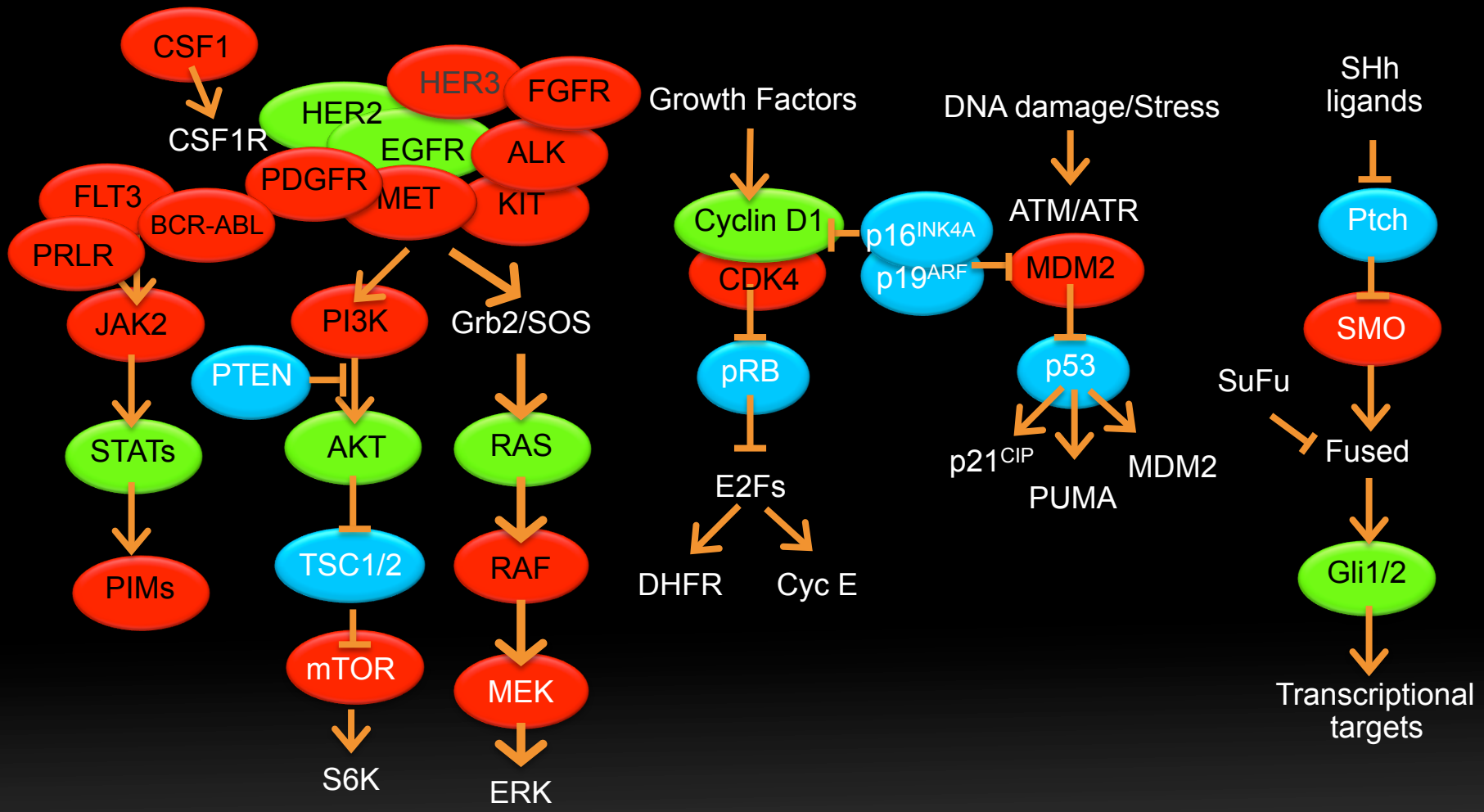
#1. We do not know the complete compendium of genetic alterations in cancer.

#2. Most known genetic alterations have not led directly to a drug candidate.

#3. Resistance develops to targeted agents.

#4. One drug is never enough.

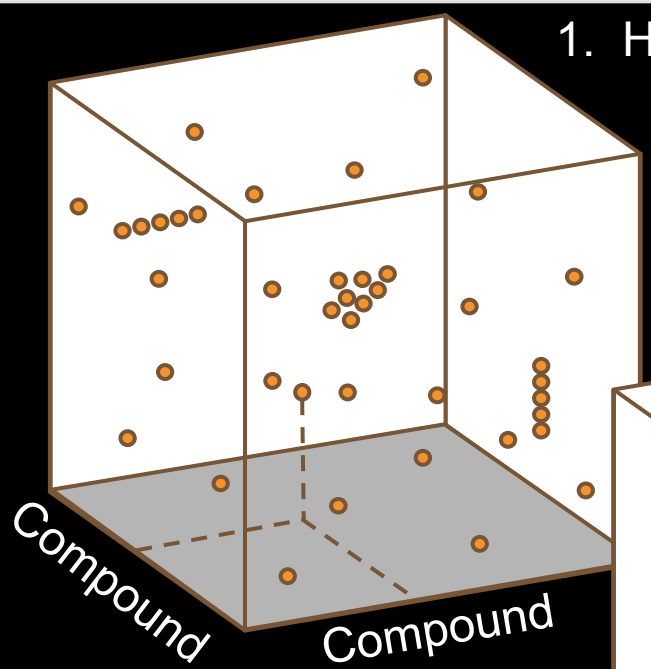
Problem 4: Discovering highly effective combinations



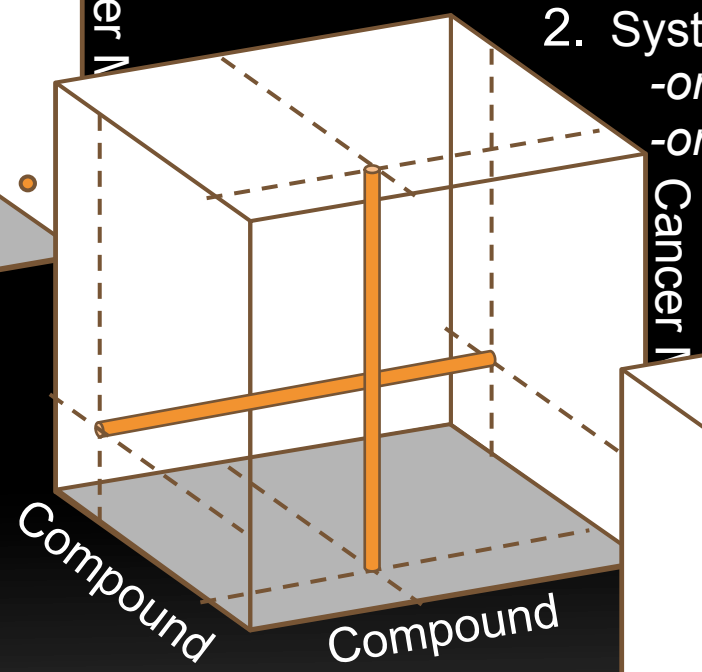
Targets of Novartis drugs in human trials

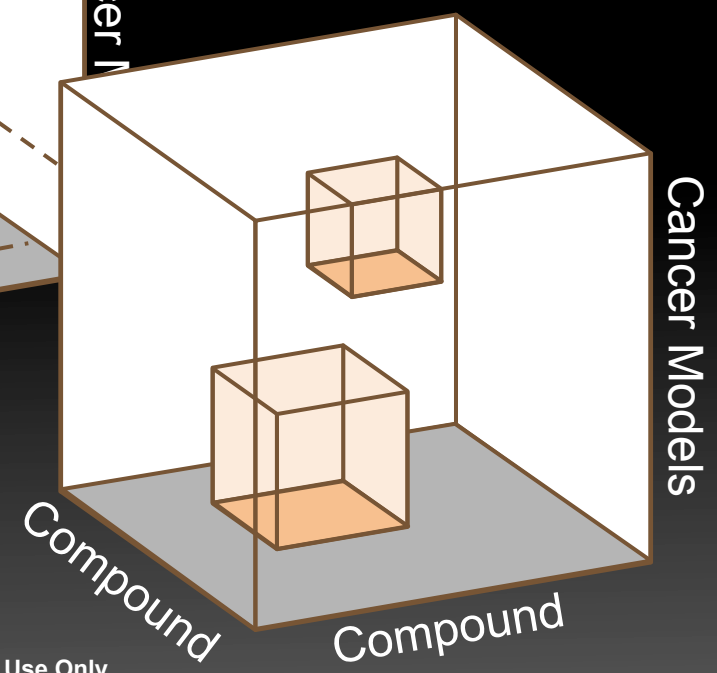
Ways to Explore the Combination Space

1. Hypothesis-directed combinations
   -hopefully more than "one-offs"



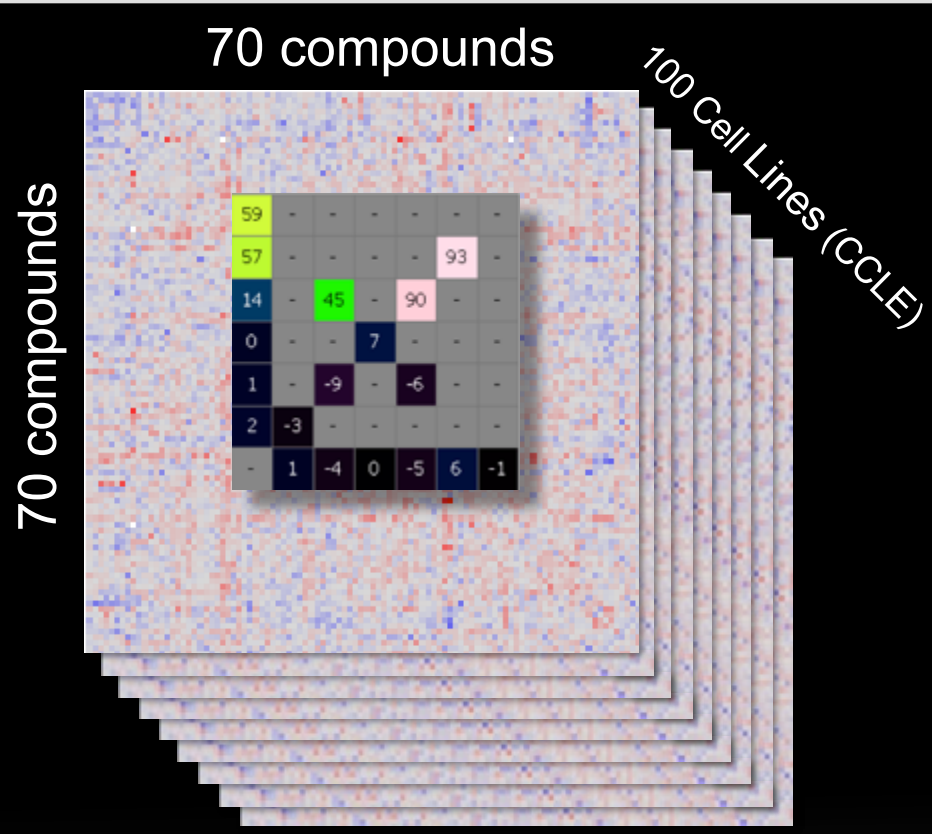
2. Systematic in one-dimension
   -one cell line x combo's
   -one combo x many lines



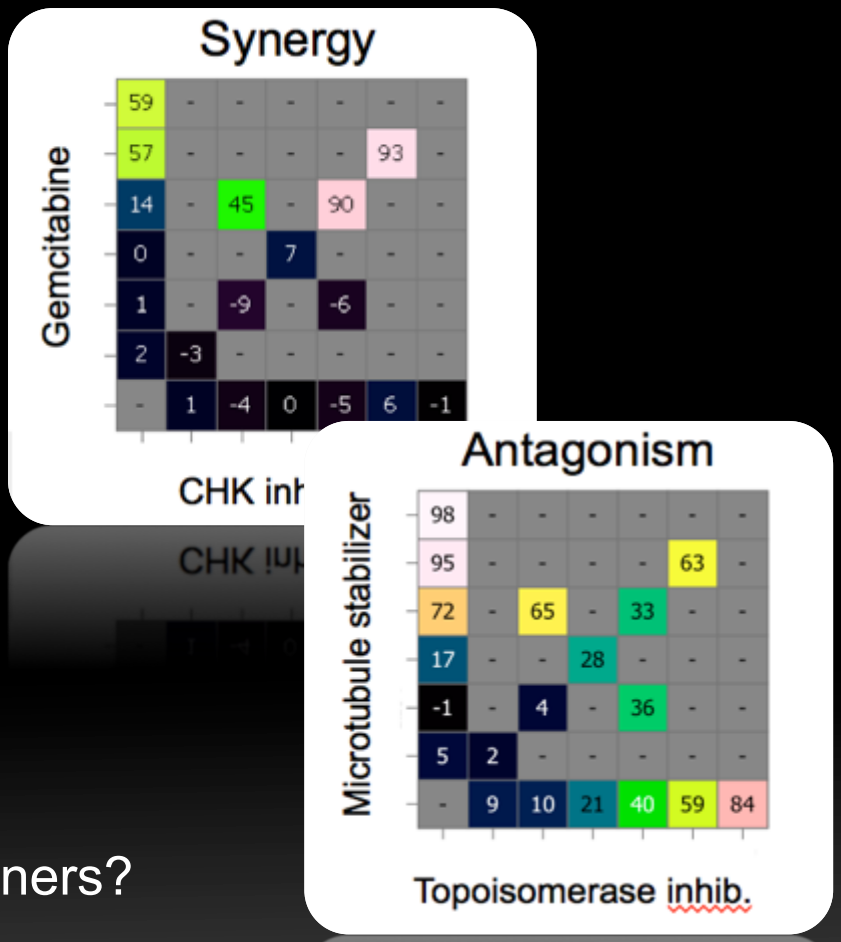


3. Systematic in three-dimensions
   -many cell lines x many combo's

Larger-scale combination screen
-collaboration with Zalicus/CombinatoRx



~27 million data points (triplicate data)



1. What are the “best” combination partners?
2. Are there underlying principles of combination therapy that can be discovered?

Two models of drug development

What are the problems or impediments to Plan B?

#1. We do not know the complete compendium of genetic alterations in cancer.

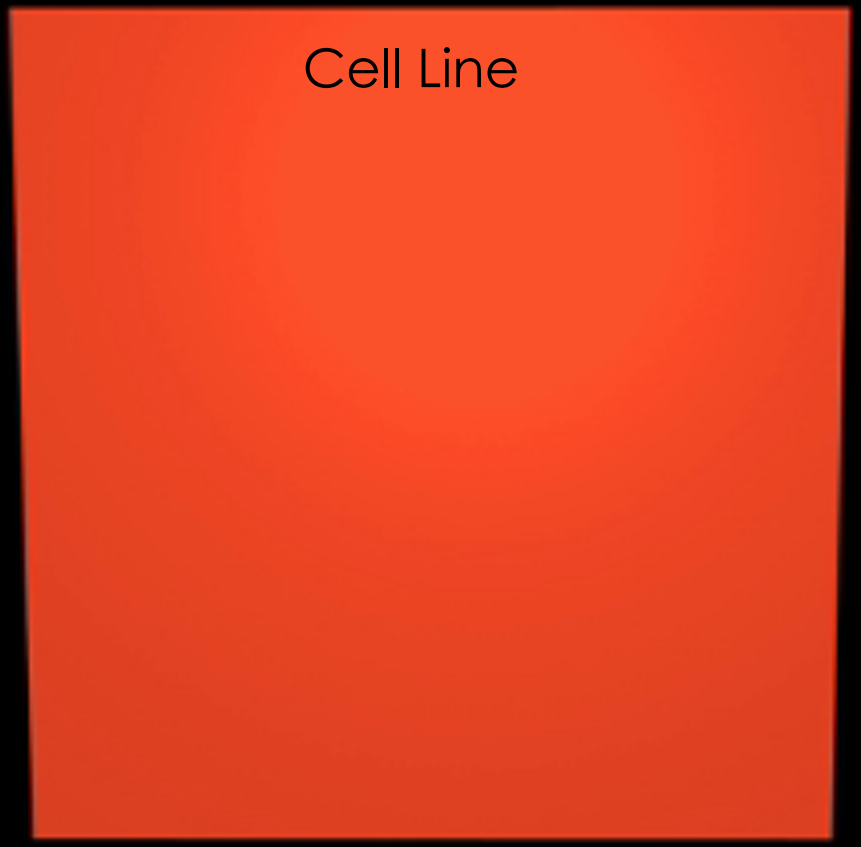
#2. Most known genetic alterations have not led directly to a drug candidate.

#3. Resistance develops to targeted agents.

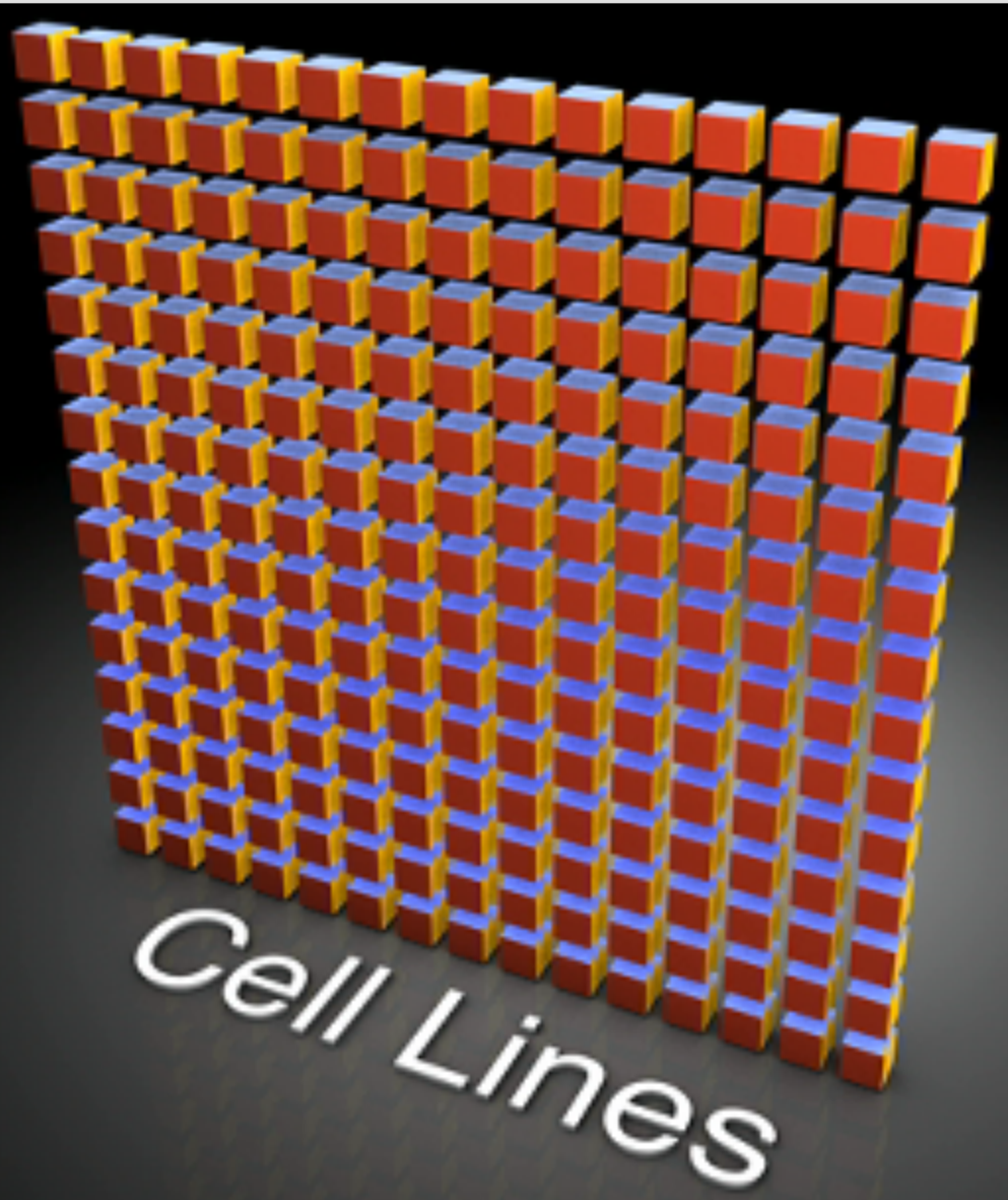
#4. One drug is never enough.

#5. Lack of a robust pre-clinical translational infrastructure.

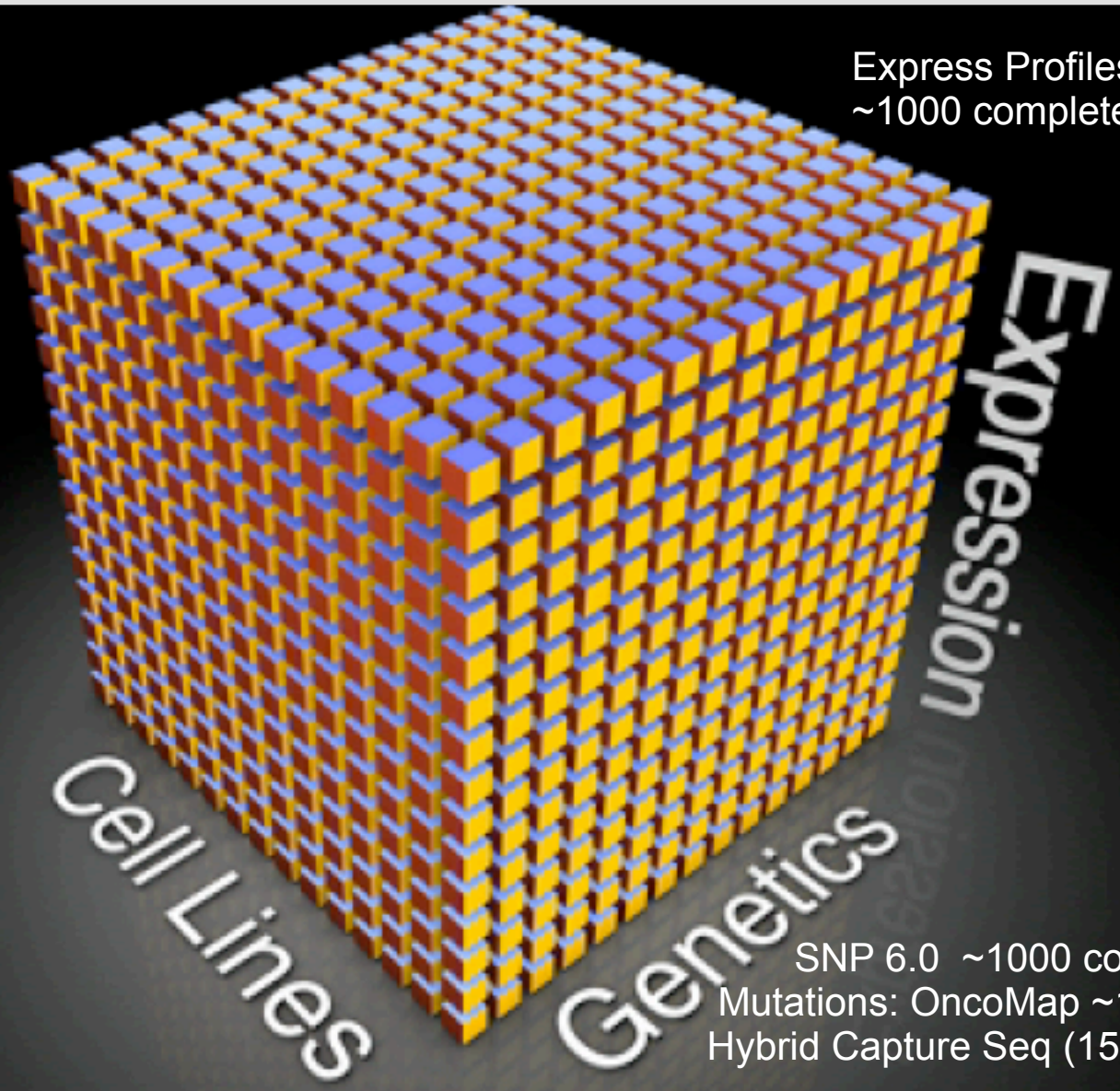
From one cell line to an encyclopedia



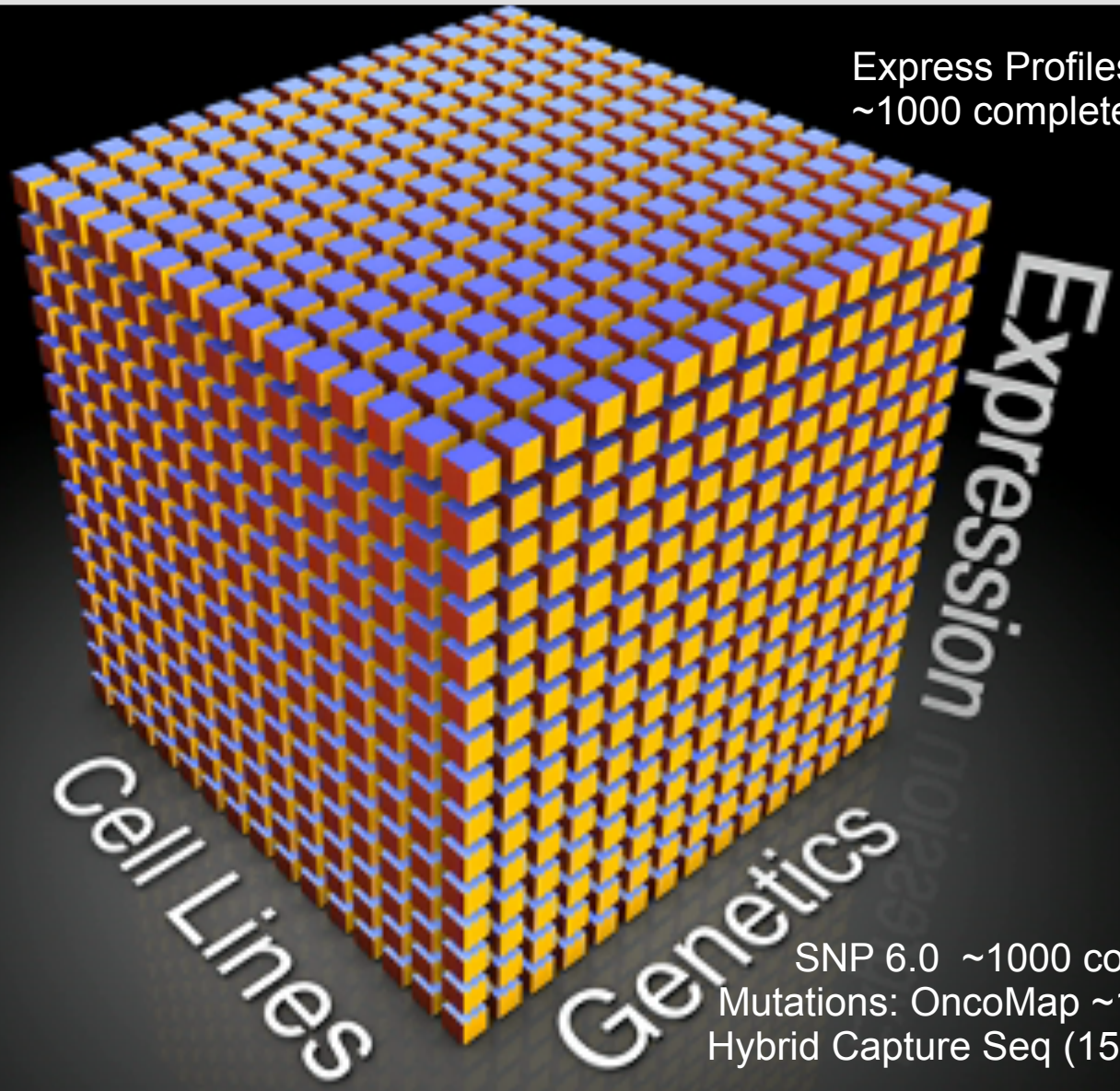
From one cell line to an encyclopedia



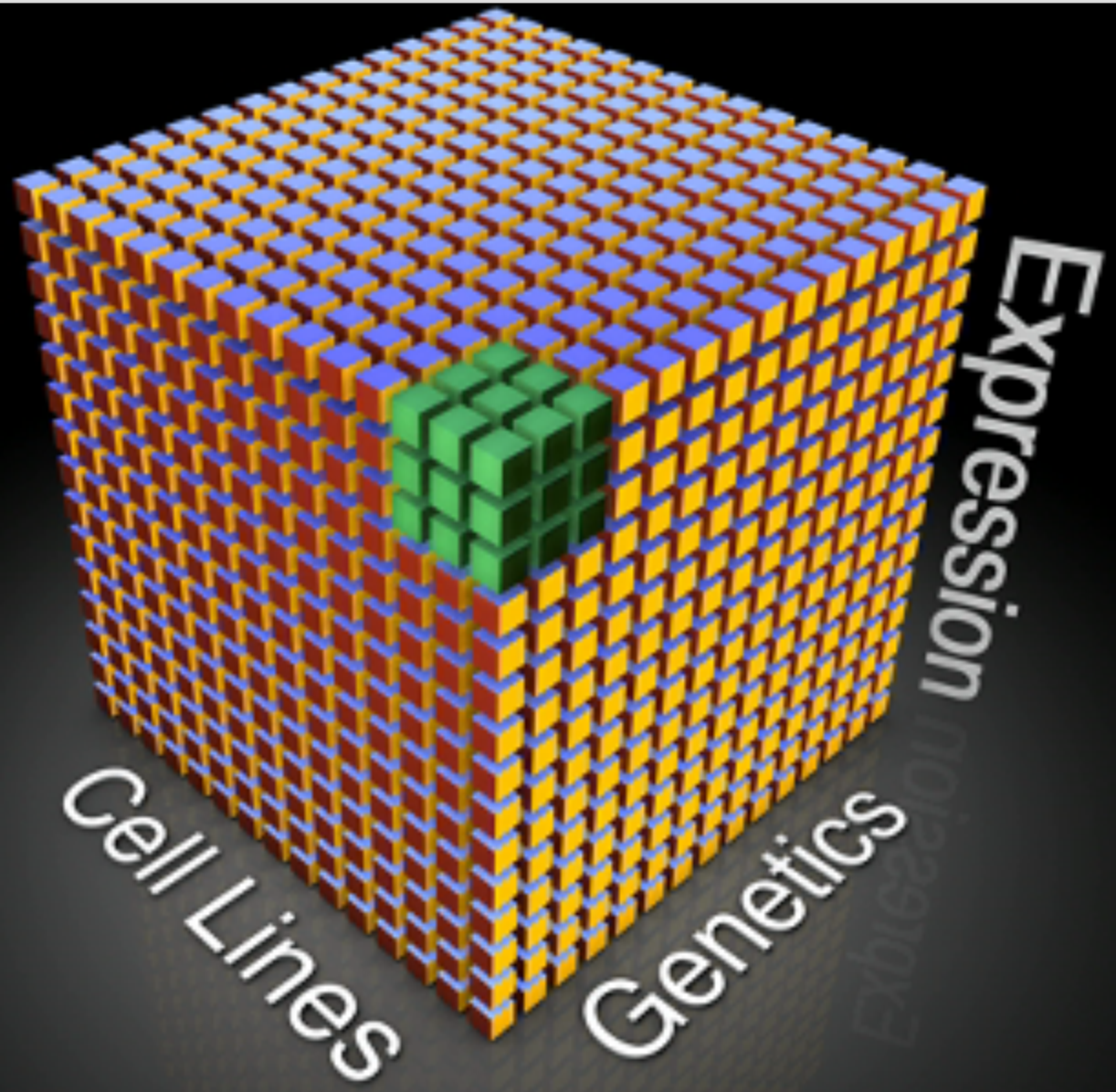
The Cell Line Encyclopedia: 1000 annotated cell lines



The Cell Line Encyclopedia: 1000 annotated cell lines

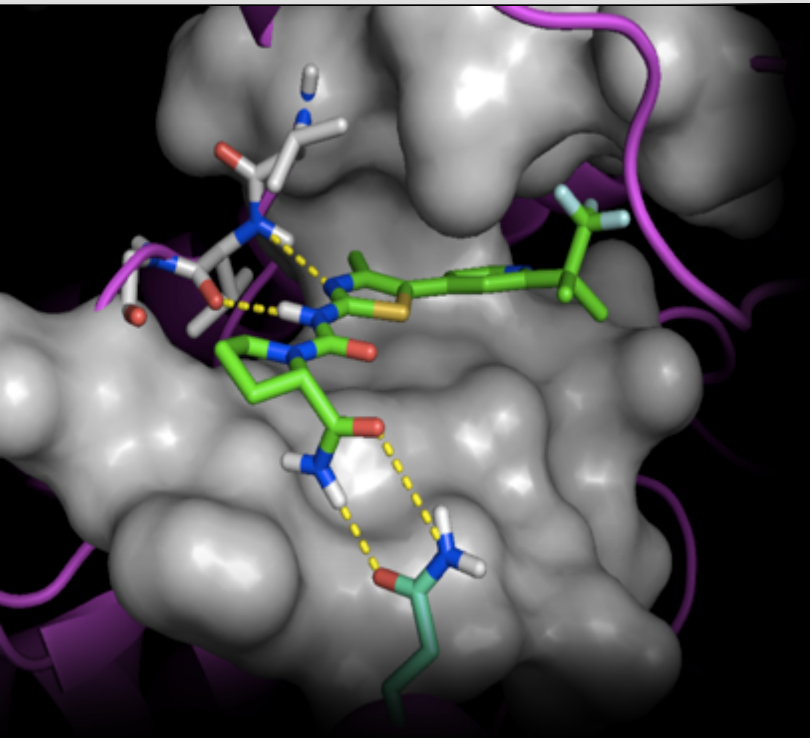


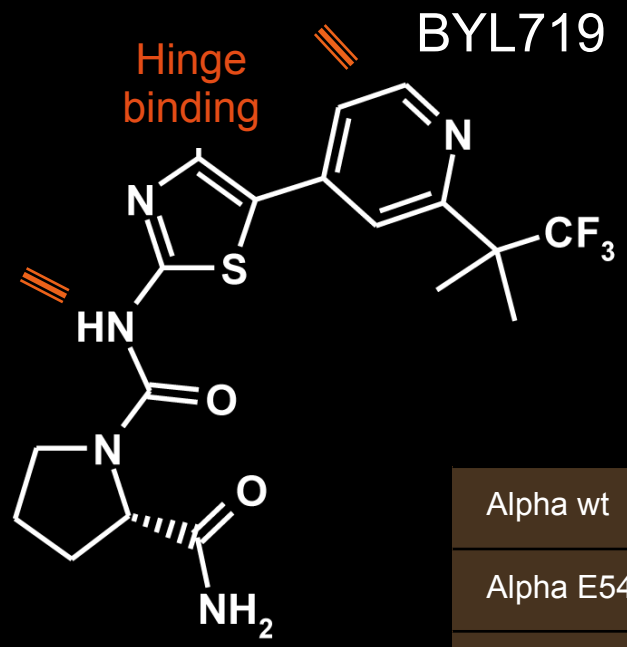
Goal: To identify predictive biomarkers for pt selection



Problem: How do we profile the “cube” ?

BYL719 Binding Mode in PI3Kalpha

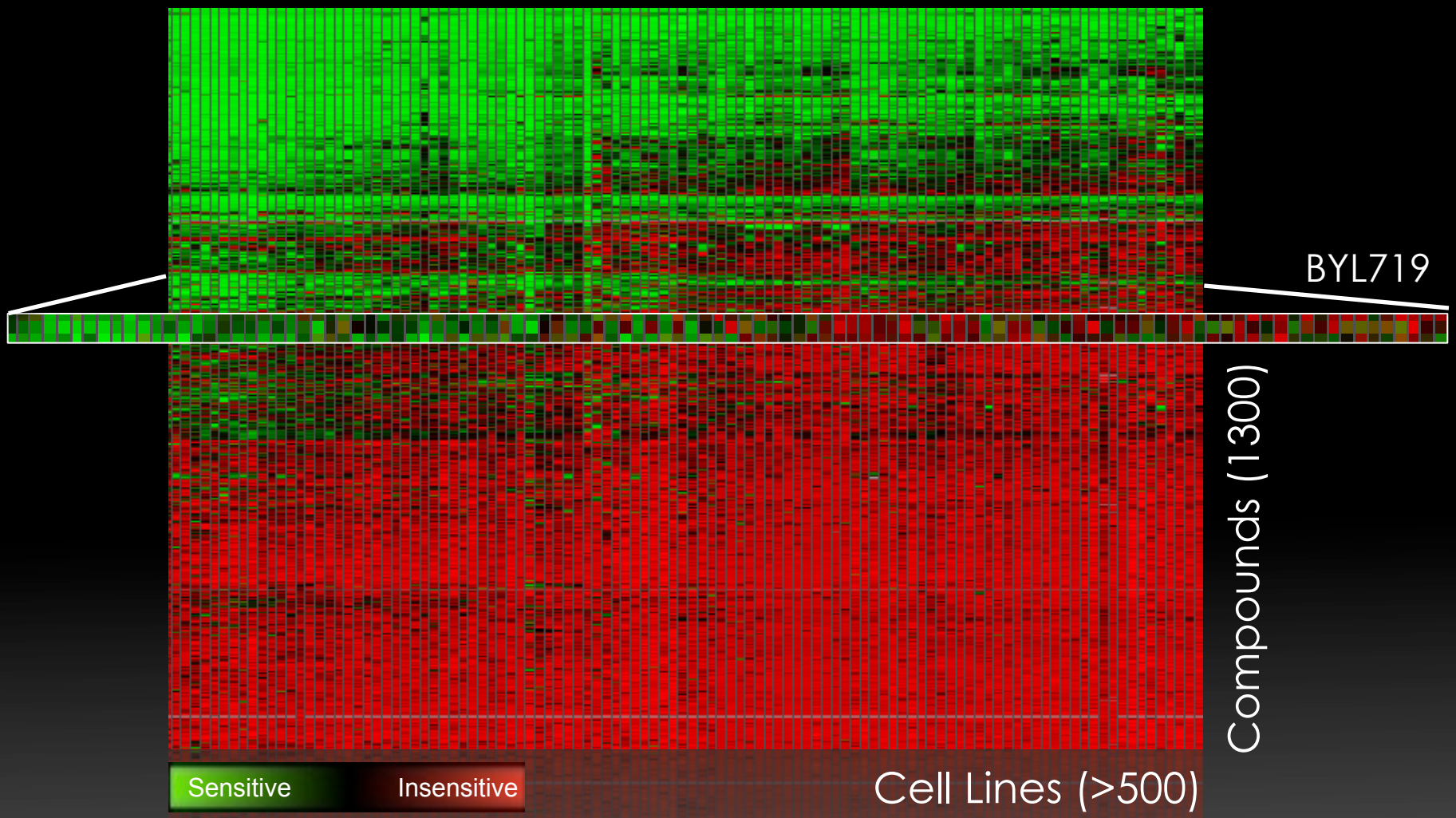




	Biochem	Cellular
Alpha wt	5	74
Alpha E545K	4	
Alpha H1047R	5	
Beta	1’156	2’249
Delta	290	1’249
Gamma	250	
Vps34	>9’100	
mTOR	>9’100	>10’000

Compound centric view of the "cube" (CLE)

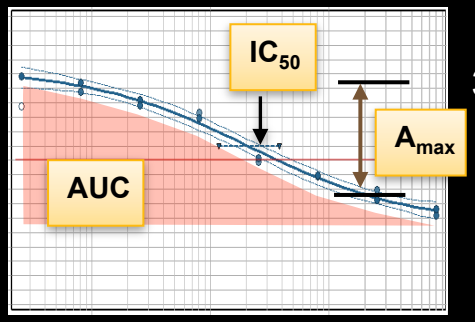
Pharmacologic sensitivity for 1300 compounds in >500 cell lines



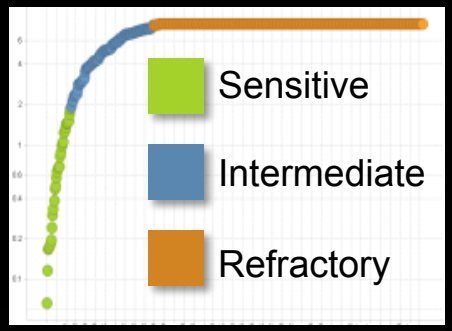
A. Huang

Known Genetic Predictors "Discovered" by Algorithms

1. Compound response



2. Sensitivity Classification



3. Molecular Features

- Lineage (Sanger annot)
- DNA Copy (Gene and GISTIC amp)
- Mutations (OncoMap, NGS)
- Expression (Affy & pathways)

Regression-based Elastic Net Model Building

Compound	Target(s)	Feature	Rank
BYL719	PIK3CA	PIK3CA Mut	1
PF2341066	MET	Met amp	3
Lapatinib	ERBB2	ERBB2 amp	1
AZD0530	Multi-kinase	EGFR mut	1
PD0325901	MEK	BRAF mut	10*
AZD6244	MEK	BRAF mut	1*
PLX4720	BRAF	BRAF mut	1
LGX818	BRAF	BRAF mut	1

BYL719 is the first PI3Kα inhibitor to enter a clinical trial

Dose Escalation Arm

BYL719 Patients with relapsing/ refractory PIK3CA mutant solid tumors (at least 21pts)	MTD (or RP2D) of single-agent BYL719

MTD Expansion Arm

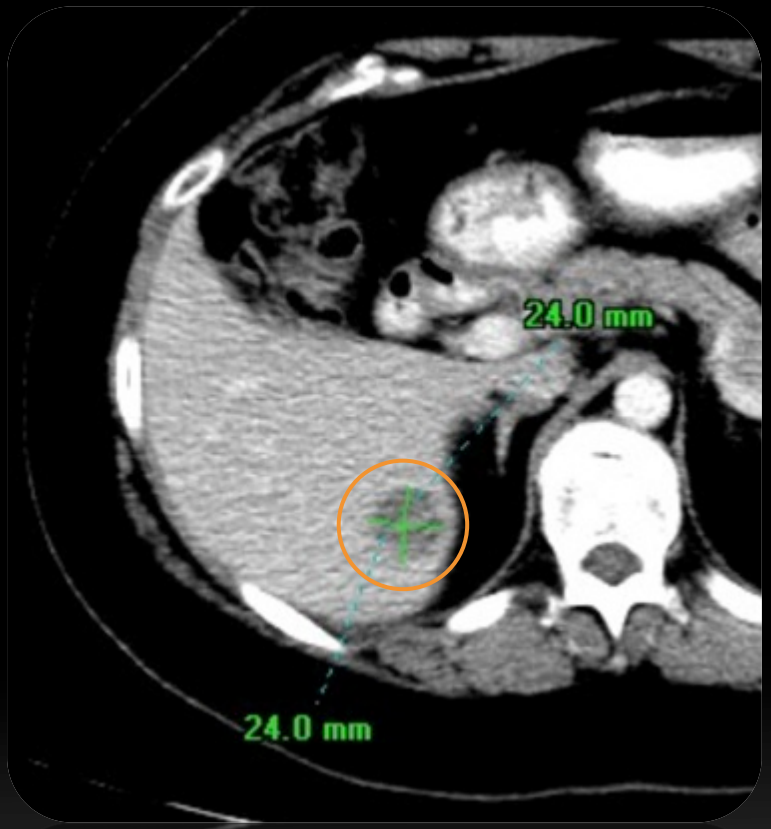
BYL719 Patients with relapsing/refractory PIK3CA mutant solid tumors (at least 16pts)

Key objective to determine MTD (or RP2D) and to evaluate safety and tolerability in patients with advanced solid tumors

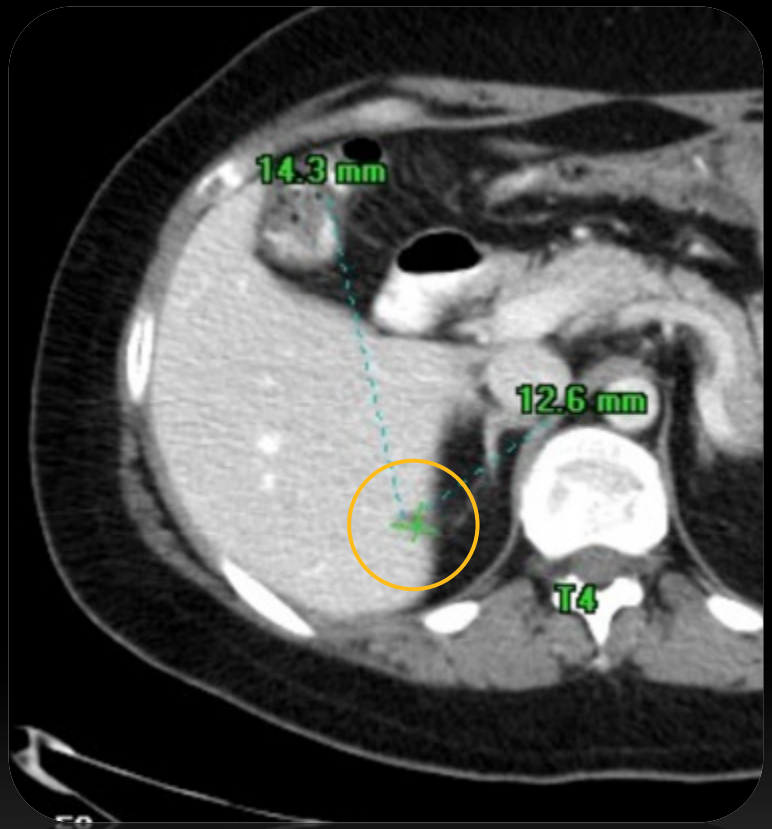
BYL719 is well tolerated

First signs of of tumor shrinkage and long-term stable disease

Response in a patient with PIK3CA^{mut} ovarian carcinoma



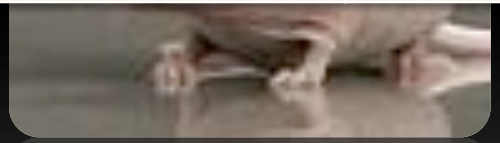
Baseline 6/2011



C2D28 8/2011

Encyclopedia 2.0 Primary Human tumor models

Molecular Annotations	Progress (tot = 410)
SNP 6.0	286
Affy U133	288
RNA-Seq	55
Whole Exome	12
2K exome	185



Implant

Tumor type	Received	Established
Colon	125	63
Lung	196	55
Breast*	362	47
Pancreas	159	52
Ovary	231	39
Sarcoma	199	47
Kidney	328	25
Melanoma	61	27
Uterus	25	10
Esophagus	21	10
Brain	49	8
Lymphoma	73	4
Stomach	43	4
Liver	56	2
Intestine	8	3
Others*	179	15
Total 2011	2115	410
Total 2010	1281	291
Total 2007	406	82

Towards curative therapy for cancer.

Disease

Pathogenesis

Target-based drug discovery

#1. Complete the cancer genome in depth.

#2a. Work on validated difficult to drug targets.

#2b. Discover synthetic lethal drug targets.

#3. Study resistance pre-clinically.

#4. Discover novel highly active combinations and test them early clinical development.

#5. Build a robust pre-clinical translational infrastructure.

Acknowledgements

Thanks to the patients participating in the clinical trials I have discussed.

Thanks to a tremendous group of NIBR scientists and Novartis Oncology clinicians who have worked on the many projects described here in.

Thanks to our many terrific collaborators.